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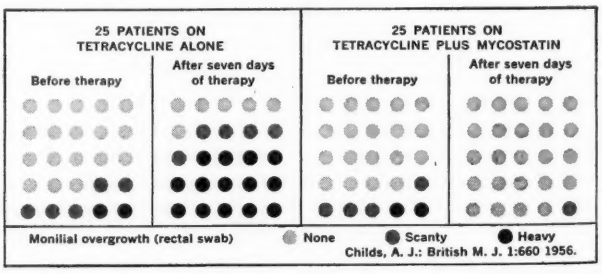

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Original Contributions

Thrombosis and the Blood-clotting Mechanism

CHARLES A. OWEN, JR., M.D.
Rochester, Minnesota

ONE OF THE MAJOR unsolved problems in the study of peripheral vascular disease is the explanation of thrombotic and embolic occlusion. It is not sufficient merely to propose that arteriosclerotic narrowing of a vessel's lumen or the slowing of blood flow explains thrombosis. Some persons who apparently have normal vessels experience occlusion idiopathically or, curiously enough, about the seventh day after an operation. Thorough analysis of the clotting mechanism of the blood in such cases might be profitable.

Because studies of abnormalities of blood coagulation have been limited traditionally to the hemorrhagic diatheses, little is known of the mechanisms contributing to thrombosis. In fact, most of the methods for study of clotting are developed about the principle of maximal acceleration of clotting *in vitro* to reveal any suggestion of retardation in one or another of the steps in clotting. As a result, if clotting is accelerated in certain thrombotic states, present methods are not likely to discover the fact.

TABLE I. SCHEME OF BLOOD CLOTTING

Platelets + AHG + PTC + PTA	(1) →	Plasma thromboplastin	+	Ca++ + Labile factor + Stable factor + Stuart factor	(2) →	Activated thromboplastin	
Activated thromboplastin + Prothrombin	(3) →	Thrombin		+ Fibrinogen + Antithrombin	(4) → (5) →	Fibrin Metathrombin	
Fibrin + Fibrinolysin	(6) →	Soluble degradation products of fibrin					

Acceleration of the clotting cycle is theoretically possible and might well lead to intravascular thrombosis. If one adds oxalate to freshly drawn, normal human blood and removes the erythrocytes by brief centrifugation, leaving the platelets suspended, this plasma will clot in about 100 seconds at 37° C. on addition of a solution of a salt of calcium. How are these 100 seconds used up in the clotting mechanism? A scheme of clotting is necessary to arrive at an answer (Table I). The first four steps shown in the table are apparently essential to clotting; steps 5 and 6 have to do with quenching the reaction.

As just indicated, the first four steps in the clotting of normal human plasma at 37° C. occupy about 100 seconds. If the plasma thromboplastin that is formed physiologically in step 1 is replaced with tissue thromboplastin (the functions of these two types of thromboplastin are apparently identical), the plasma will clot in twelve seconds. This procedure, of course, is what is done during the Quick "prothrombin time" test performed with an extremely active extract of brain. Thus, elimination of the first step of clotting shortens the clotting time of the plasma from 100 to twelve seconds. Therefore, the complex interactions between platelets and the various hemophilic factors, namely antihemophilic globulin (AHG), plasma thromboplastin component (PTC) and plasma thrombo-

Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 23, 1957.

From the Section of Clinical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

plastin antecedent (PTA), occupy seven-eighths of the entire clotting process. By contrast, the second, or co-thromboplastin, step takes about six seconds, and steps 3 and 4 take the remaining six seconds.

If one is permitted to extrapolate these *in vitro* data to clotting *in vivo,* it becomes obvious that minutes to hours normally are required for the generation of plasma thromboplastin. Anything that might accelerate this first step, such as breakdown of platelets, or might eliminate this step, as the introduction of tissue juices into the blood stream, might induce clotting faster than the protective mechanisms—antithrombin (step 5) and fibrinolysin (step 6)—could function. Thus, thrombosis might be considered as the product of accelerated clotting *in vivo.*

Of course, the term "accelerated" presumes that clotting is occurring normally within the blood vessels, even if extremely slowly. There is reasonable likelihood that this does happen. The various clotting proteins that have been studied, namely, antihemophilic globulin, labile factor, stable factor, prothrombin and fibrinogen, all leave the blood stream at a much faster rate than do the major protein components of the plasma. Thus, negligible AHG remains in the blood of a hemophiliac patient twenty-four hours after a transfusion of fresh blood or plasma; the other clotting factors disappear rapidly after their source, which is the liver, has been removed from animals. It is unlikely that these clotting proteins are merely being metabolized in a nonspecific manner; it appears more reasonable that they are being consumed by clotting.

It is difficult, at first, to accept this hypothesis (by no means new) that clotting occurs continuously in the body, because one cannot find fibrin, which is the evidence of clotting, within the peripheral vessels or the lungs. However, fibrinolysin, which is the potent clot-dissolving enzymatic system of the blood, is presumably the scavenger that prevents traces of clotting from becoming thrombosis.

It may not be wise to condemn the theory of continuous intravascular coagulation just because fibrin cannot be seen. A classic experiment is the extremely slow injection of thromboplastin into the blood stream of an animal. When such a procedure is correctly performed, it is possible to convert the animal's plasma to serum, including complete loss of fibrinogen. Despite this, postmortem identification of fibrin is difficult or impossible.*

The well-recognized prophylactic and therapeutic effects of heparin and of dicoumarin derivatives furnish suggestive evidence that artificial retardation of clotting may compensate for a state of hypercoagulability. Further, the more rapid dissolution of an established clot during anticoagulant therapy suggests that a delicate balance exists between the formation and the lysis of fibrin that can be tipped in favor of the latter process by depressing the former.

Unfortunately, few factual data are at hand to support these various conjectures. It appears unlikely that much improvement in this situation will occur until new laboratory methods are designed that are directed at accelerated rather than at retarded clotting systems.

*The obvious human analogy is the hemorrhagic tendency that is associated at times with abruptio placentae and that is inaccurately described as "afibrinogenemia." Since the loss of fibrinogen is secondary to coagulation of the blood, which in turn is the result of introduction of thromboplastin into the blood stream, the term "thromboplastinemia" more nearly describes this coagulation state.

BOOKLETS PUBLISHED FOR PATIENTS ON SODIUM-RESTRICTED DIETS

Three new booklets prepared especially for adult heart patients placed on sodium-restricted diets by their physicians have been published by the American Heart Association.

The booklets are available to physicians for distribution to their patients. They are also being made available to patients by local Heart Associations on a physician's prescription. Copies may also be obtained by nurses, nutritionists, dietitians and hospital and nursing home staffs.

The new booklets were prepared under the direction of a committee representing four agencies in addition to the American Heart Association. They are the U. S. Public Health Service, the American Dietetic Association, the Council on Foods and Nutrition of the American Medical Association, and the Nutrition Foundation.

Each booklet is designed to help patients follow the physician's prescription for a different degree of sodium restriction: strict, 500 mg.; moderate, 1,000 mg.; and mild. Within each booklet, there is a choice to be indicated by the physician, of three different calorie levels, 1,200 calories, 1,800 calories and unrestricted. Food lists enable the patient to vary his meals as he becomes familiar with his basic diet plan. Weight watching, meal planning and problems of the family cook are discussed and practical suggestions on eating out and shopping for food are given.

Diet, Physical Activity and the Serum Cholesterol Concentration

HENRY LONGSTREET TAYLOR, Ph.D.
Minneapolis, Minnesota

MORRIS[1] has reported that, in England at least, coronary heart disease occurs less frequently in physically active men than in their sedentary contemporaries. This finding has been confirmed by Brown et al[2] in a survey of men in the seventh decade who happened to be on the lists of eleven practitioners in Birmingham, England. These reports make the effects of physical activity on the level of serum cholesterol of some interest.

There are a number of factors which are known to influence the level of serum cholesterol, the most important being diet and sex hormones. Since exercise with its demands for calories influences the diet, it will be useful to discuss in detail the dietary factors which are known to be important in the regulation of cholesterol metabolism before taking up the specific effects of exertion.

Of the several dietary parameters which might affect cholesterol metabolism in man, the caloric balance,[3-5] the quantity of dietary fat[6-9] and the type of fat consumed[10-13] have been shown to be important factors affecting the level of serum cholesterol concentration. It has been customary for experimental investigators in this field to study the effects of alteration in the proportion of fats in the diet or to vary the total number of calories consumed, holding the energy expenditure and the amount of physical activity reasonably constant. Experiments of this kind and the study of the relationship between serum cholesterol levels and the composition of the habitual diet in population groups have led to the conclusion that when the quantity of fat is varied in ordinary human diets without changing the proportions of the several kinds of fatty acids in the fat, the percentage of calories derived from fat is the important factor in controlling the serum cholesterol concentration. If one holds the number of calories derived from fat constant along with the caloric expenditure and then feeds subjects fats which contain variable amounts of linoleic acid, it is found that fats with large quantities of linoleic acid depress the serum cholesterol concentration and fats which are made up of large proportions of saturated fatty acids produce increases in serum cholesterol concentration. This relationship is sufficiently constant to make it possible to predict with considerable precision the change in serum cholesterol concentration which will be produced by a change in either the amount and/or type of fatty acids in the diet.[13]

The caloric balance is an important factor which can have marked effects on the serum cholesterol concentration. A negative caloric balance will produce a fall in the serum cholesterol concentration,[3] while on the other hand, a positive caloric balance will produce an increase in serum cholesterol concentration.[4,5] It also follows that calorie equilibrium must be maintained if relative stability of the serum cholesterol concentration is to be maintained.

It is against this background of rather complex nutritional control of serum cholesterol that one must assess the effects of exercise.

The acute effects of exercise were studied in the Laboratory of Physiological Hygiene some time ago.[14] The results are summarized in Table I. In series A and B, cholesterol determinations were carried out in duplicate before and two hours after a breakfast which included eggs and heavily buttered toast. The value obtained after breakfast was subtracted from that obtained before breakfast and the difference is recorded in the

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Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 23, 1957.

From the Laboratory of Physiological Hygiene, The School of Public Health, University of Minnesota, Minneapolis, Minnesota.

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table. Series A differed from series B in that the serving of eggs contained 10 grams of cholesterol. In series C, breakfast was followed by moderately vigorous physical activity (walking on the treadmill or working in the garden). The fat-loaded meal in series A and B was followed by a small but significant rise in the serum cholesterol concentration while in series C the exercise resulted in a definite decrease. Combining the data, we can say that the effect of exercising after the fat-loaded meal was to reduce the serum cholesterol concentrations by 8 mg. per 100 ml. of serum. This result is statistically highly significant since the standard error is only ± 2.25 mg. per 100 ml. of serum.

TABLE I. THE EFFECTS OF EXERCISE ON THE CHANGE FROM THE BASAL STATE TWO HOURS AFTER A HIGH FAT BREAKFAST IN THE SERUM CHOLESTEROL CONCENTRATION ON MG. PER 100 ML.

Series	Post Meal Conditions	N.	Mean (△)	S.D. (△)	S.E. (△)
A	Sedentary	51	4.92	±11.72	±1.66
B	Sedentary	73	3.95	±11.74	±1.37
C	Exercise	15	−3.93	±12.95	±3.34

Experimental evidence of the effects of changing the level of daily exercise was provided by Mann and his co-workers[5] in the Harvard School of Public Health. These investigators examined the effects of increasing the calorie requirements of three men from 3,000 to approximately 6,000 calories a day by adding an intensive regimen of physical activity. The 3,000 additional calories were eaten in the form of carbohydrate; no additional fat was provided in the diet. The physical activity was continued at a high level for four weeks at which point it was discontinued without changing the daily ration of 6,000 calories of food. Table II shows the results obtained by Mann and his co-workers. During the period of increased physical activity, there was no change in the serum cholesterol concentration. The period of excess calories clearly demonstrated that a positive caloric balance results in an increased serum cholesterol concentration. Similar results have been obtained in this Laboratory.[4] Mann and his colleagues have interpreted this to mean that exercise prevented the increase in serum cholesterol during the activity period.

The effects of exercise in this experiment were not as clear-cut as one might like since the subjects were not able to burn up all the calories provided in the diet and consequently gained weight. Thus, there was a situation which, other things being equal, would be expected to result in an increase in serum cholesterol present. On the other hand, adding to the daily diet 3,000 calories in the form of carbohydrate resulted in a decrease in the percentage of calories derived from fat, a change which one would expect to result in a decrease in serum cholesterol under conditions of constant physical activity.

TABLE II. DATA OF MANN ET AL.[5] ON THE EFFECTS OF INCREASING THE DAILY PHYSICAL ACTIVITY BY 3000 CALORIES

Item	Control Period	Exercise Period	Excess Cal. Period
Time	2 weeks	4 weeks	4 weeks
Cal./day	2934	6000	5740
Fats as % cal.	52	26.1	27.4
Body weight	183	188.5	199
Serum cholesterol	180	178	230

In the Laboratory of Physiological Hygiene the effect on the serum cholesterol concentration was studied in the presence of several separate diets. The experiments were carried out in a standard situation and one of these experiments has been reported in detail.[15] In each case, the experimental design included a sedentary control period of two weeks. This was followed by a training period usually lasting a week or so in which the men accustomed themselves to walking for a period of two hours on the motor driven treadmill set at a grade of 10 per cent and a speed of 3.5 miles per hour. This activity required 1,200 calories a day and was maintained for not less than two weeks in addition to the training period in each experiment. The activity period was followed by a second sedentary period lasting from ten days to two weeks in which the diet was identical to that in the control period. Particular attention was paid to the maintenance of a constant body weight.

At the end of each period, blood was drawn on two successive mornings before breakfast. Each sample was analyzed in duplicate for total cholesterol and for the cholesterol associated with α and β lipoprotein. Total fats, non-esterified fatty acids, and phospholipids were analyzed to complete the picture.

In each experiment, 300 calories a day were allowed for calories that would be consumed

by metabolism required by activities that would have been undertaken in the two hours devoted to treadmill work. The caloric cost of the exercise was then payed off with approximately 900 calories of food. The fat content of the food used to pay for the exercise was the item which was varied. In each case, great care was taken to ensure that the relative proportions of saturated to unsaturated fats remained constant in both the control period and the exercise period. Therefore, the principal variable here is the per cent of calories derived from fat. In the first experiment, the proportion of fat derived from calories in the food added in the exercise period was identical to that used in the control period. This resulted in the proportion of calories derived from fat being held constant in the three periods but the total amount of fat consumed by the men was increased during the exercise period. In the second experiment, the additional calories were 100 per cent fat, thus raising both the total fat ingested and the proportion of calories derived from fat during the exercise period. And finally in the third experiment, the added calories were 100 per cent carbohydrate, thus decreasing the per cent of calories derived from fat and holding the total amount of fat constant. The principal findings along with the dietary conditions are presented in Table III.

TABLE III. THREE EXPERIMENTS ON THE EFFECT OF INCREASING THE DAILY PHYSICAL ACTIVITY LEVEL ON THE SERUM CHOLESTEROL CONCENTRATION
(For explanation see text)

Exp. No.	No. of Subjects	Control Period			Exercise Period Additional Calories			Exercise Period Total Calories			Body Wt. △ in Pounds	Mean Serum Cholesterol mgms./100ml.		
		Total Cal.	Fat Grams	Fat % Cal.	Exercise Cal.	Fat Grams	Fat % Cal.	Total Cal.	Fat Grams	Fat % Cal.		Control	Exercise	Recovery
1	9	3250	155	43	930	46.0	44	4190	201	43	+0.60	158.3	159.8	161.5
2	5	3200	143	40	920	102	100	4120	245	53	+0.2	196.6	198.1	198.5
3	7	3200	145	41	900	0	0	4100	145	31.8	+0.35	199.5	181.1	195.8

It will be observed that increases of 46 and 100 grams of dietary fat a day were tolerated by the men during the exercise period without any appreciable increase in the serum cholesterol concentration. Elsewhere,[13] it has been shown that under conditions of constant caloric intake and fat composition, the percentage of the total calories derived from fat is the important controlling factor. If exercise did not modify the effects of diet, it would be predicted that the serum cholesterol concentration would remain unchanged in Experiment One, increase in Experiment Two and decrease in Experiment Three. In actual fact, it was predicted in Experiment Two on the basis of a prediction equation[13] derived from experimental work in which the composition of the diet was changed holding physical activity and total caloric intake constant that the serum cholesterol concentration would increase 28 mgs. per 100 ml. of serum in the group of men studied. Keys et al[13] did not study diets which contained as much fat as this, so the accuracy of the predicted value may be in some doubt, but there can be no question that increasing the percentage of calories derived from fat from 40 to 50 would be expected to result in a demonstrable increase in serum cholesterol concentration. We may conclude that within the range of fat content of diets studied, exercise allows a man to handle a large increase in the fat transport load without any comparable increase in serum cholesterol concentration and that it can alter the expected response of the serum cholesterol to alterations in the diet.

It is useful to regard the lipoprotein cholesterol complex as a vehicle for the transport of fat from one important metabolic site to another. Anderson, Lawler and Keys[4] have proposed that the observed variations in cholesterol concentration which result from dietary manipulation can be explained by the relationship between the fat transport load and the available fat transport, that is, lipoprotein cholesterol concentration per unit of circulation. The fat transport from gut to liver to fat depot was suggested as the general route involved.

Current concepts regarding the mechanism of fat transport are emphasizing two general pathways for transport.[16,17] One concept focusses on the lipoproteins, the other on non-esterified fatty acids (NEFA) but these are not viewed as mutually exclusive. It is, however, desirable to con-

sider the possible relative importance of these two mechanisms of fat transport in various situations. In the first stage of fat metabolism, the absorption of fat from the gut and transport into the central blood pool, neither NEFA nor lipoprotein transport may be very important, the newly added lipid being primarily in the form of a suspension of chylomicrons in this phase of post-prandial lipemia.

There is, of course, much support for the idea that the fats are extensively hydrolyzed in or in close proximity to the gut wall and are then reassembled as neutral fat and are transported as such in the chylomicrons that characterize the lipemic phase. And there is little doubt that much of the absorbed fat is temporarily deposited as such in the liver. It is with the subsequent events, the transport of fat from the liver to the tissues and the mobilization of fat from depots elsewhere, that we are mainly concerned.

There is good evidence that under some conditions, at least, fat transport in the lipoproteins is very important. For example,[18] infants suffering from the general protein deficiency represented in kwashiorkor have grossly enlarged livers loaded with fat and very low levels of blood cholesterol from which we infer similarly low levels of lipoproteins in the blood. When such infants are treated simply by feeding proteins or even only a mixture of amino acids, the liver very rapidly loses its fat, the subcutaneous fat depots are repleted and in the process the blood serum cholesterol may rise in a few days from a pre-treatment value of 50 mg. per 100 ml. to one of 250, only to decline to more normal values in the region of 100 when this rapid transport of fat from liver to tissue ceases. The inference is that lipoprotein is importantly involved in this transport of fat.

On the other hand, large movements of fat from the depots to working muscles occur with no corresponding rise in cholesterol or lipoprotein concentration in the blood and there may even be a fall. We observed[19] that when young men are performing 1,100 calories of work a day and are fed only a diet of 1,010 calories of carbohydrate, the serum cholesterol concentration fell to 88 per cent of the control value in spite of the fact that large amounts of fat were clearly being transported from the depots to the sites of combustion.

Such evidence as the latter points to a second important mechanism of fat transport, one that would be capable of following large changes in metabolic requirements quickly. The second mechanism for fat transport which is currently being postulated is of this general type. It has been demonstrated that the non-esterified fatty acids are rapidly mobilized when the carbohydrate supplies are inadequate;[17,20,21] that it can account for as much as 70 to 90 per cent of the metabolism of cardiac muscles[17-20] and that it is mobilized from fat depots for utilization in other tissues.[20] Unfortunately no observations on non-esterified fatty acids were made in the semistarvation experiment referred to above but the evidence makes it a reasonable hypothesis to suggest that the non-esterified fatty acids played an important role in the large fat transport that must have taken place.

Let us for a moment return to the hypothesis that the lipoproteins play an important role in transport of fat from liver to fat depot or tissues. If this hypothesis holds, then any increase in fat load to be transported over this route without an increase in the circulation rate will result in an increase in the lipoprotein concentration. A decrease in the fat load with no change in circulation will result in a decreased lipoprotein concentration. Conversely, if the circulation is changed with no change in fat load, the concentration of lipoprotein will be inversely related to the changes in circulation. Finally, the changes in lipoprotein concentration will be reflected in the changes in serum cholesterol concentration provided the lipoprotein cholesterol complex remains reasonably constant in chemical composition.

In this form the theory appears to be consistent with the following observations:

1. When a positive caloric balance is present, the serum cholesterol concentration increases (increased transport of fat from liver to fat depots, only small changes in the circulation. Note that the excess calories may be principally carbohydrate).

2. The fall of cholesterol concentration in the serum cholesterol when a negative caloric balance is present (decreased fat transport from liver to fat depots, some decrease in circulation, the decrease in serum cholesterol is relatively small).

3. The increase in serum cholesterol concentration when the proportion of fat in the diet is

increased, caloric intake remaining constant (increased fat transport from liver to depots, no change in the circulation).

4. The relative stability of the serum cholesterol concentration when men are in caloric equilibrium on a diet of constant composition (transport load constant, circulation constant).

5. The decrease in serum cholesterol when the proportion of fat in the diet is reduced (a reduced fat load transported from liver to depots, no change in circulation).

In the exercise experiments reported here, the rate of metabolism is quite large during the actual work. The average oxygen intake is 2.2 liters per minute which means 10 to 11 calories a minute depending on the respiratory quotient (R.Q.). At an R.Q. of 0.85, approximately 5 calories a minute must be supplied by fat. It is reasonable to assume that such calories are supplied by either fat present in the muscle before exercise begins or fat transported to the muscle during exercise probably in the form of non-esterified fatty acids. Experimental work[22] in this Laboratory indicates that in steady state exercise lasting one hour the non-esterified fatty acids are close to the exercise starting level. But when work stops the concentration of the non-esterified fatty acids increases, on the average, 0.5 milleequivalents per liter with the first ten minutes and that this increase disappears after thirty to forty minutes. This strongly suggests that the rate of production is increased during exercise and that the piling up of non-esterified fatty acids in the blood is the result of a continuing production at a high level coupled with a decrease in utilization.

The implied conclusion resulting from Experiment One[15] that the lipoprotein cholesterol complex took part in transporting fat to the muscles in exercise appears to be incorrect in the light of Experiment Two. A more acceptable hypothesis would appear to be that the non-esterified fatty acids provided much of the fat transport during exercise. The findings presented here would appear to be consistent with the hypothesis that the lipoprotein cholesterol transport system can be largely bypassed during exercise. In the experiments under consideration, the exercise took place in a comparatively short time. If one is to judge by the slow increase in the cholesterol concentration after imposing a heavy fat load without changing the caloric requirement, fat transport by the lipoprotein cholesterol system is a slow but probably continuous process. The circulation between liver and skin or other fat depots is probably not much influenced by such a short intensive bout of exercise. The results of Experiment Three can be reconciled to the view presented here if one assumes that the exercise consumed enough fat to reduce the fat transport load from liver to fat depot while in Experiments Two and Three this was little affected because of the additional fat offered in the diet.

The view presented here suggests that the relation of exercise to meals may be important and that exercise at a lower rate spread over a longer period of time may have somewhat different effects.

Summary

It is clear that a number of questions have yet to be answered regarding the effects of exercise on the serum cholesterol concentration. Nevertheless, it can be stated that physical activity can allow man to increase the total quantity of fat ingested without a parallel increase in the serum cholesterol concentration and that exercise can alter the response of the serum cholesterol to dietary manipulation. The nature and extent of the alteration remain to be worked out. A theory which revolves around the transport of fat for storage and metabolic purposes is discussed in relation to new findings.

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Connective Tissue Changes Which May Be Related to Aging and Atherosclerosis

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THE PROBLEM of aging and atherosclerosis is assuming an ever-increasing prominence in this twentieth century society, for not only are the complications of atherosclerosis becoming painfully clear but the young and highly productive individuals of our population are being affected.

Most of the investigation into the problem of aging and atherosclerosis is in its initial stage. Our laboratories find themselves at the beginning of research into the tissue which appears to be altered perhaps as the initial event of the aging process. I wish to report to you on the work that has been completed in the study of connective tissue as it might pertain to these processes. The research opportunities to be found in connective tissue are vast and extremely exciting and they involve many diverse biochemical, physical chemical and immunochemical interests.

To orient thinking in regard to the aging blood vessel, it might be worthwhile to itemize information which is accepted by workers in this field.

Effects of Aging upon Vascular Tissue

(1) General
  (a) Internal elastic lamella becomes frayed, duplicated and replaced with collagen
  (b) Intima becomes thickened with collagenous tissue
  (c) Reduction in elastic properties of vessels occurs
(2) Coronary arteries
  (a) Intimal layer of coronary artery increases in size, particularly in males
  (b) Intimal thickening is greater in the left coronary artery than in the right
(3) Cerebral arteries
  (a) Intimal thickening and endothelial proliferation occur

Early in life, blood vessel changes which are ascribed to aging can be seen. The work of Moon and Rinehart[1] indicated that intimal thickening and fraying of the internal elastic lamella occur in infants a few months of age. A graph of the changes of the intima and the internal elastic lamella of the coronary arteries against the age of humans, revealed that these alterations occur early in life and reach their near maximum in the mid-thirties.

The arterial vessels of the body differ in fibrous protein composition.[2] The thoracic aorta is made up predominately of elastic fibers, but as the aorta passes through the diaphragm, a marked alteration in composition is observed. The abdominal aorta is made up of 70 per cent collagen and only 30 per cent elastin. The collagen-to-elastin ratio observed in the abdominal aorta is also seen in the peripheral vessels.

When a comparison is made between the fibrous protein composition of the arterial vessels and the early aging and atherosclerotic changes in the peripheral vessels, it is noted that the abdominal aorta, the iliacs and the coronary vessels with the greater percentage of collagen show the early changes, that is, in male patients, sixteen to thirty-nine years of age.[3]

To summarize what is known concerning the aging changes in the blood vessels, it appears that: (1) aging of an artery consists of an increase in connective tissue elements, particularly collagen; (2) vascular alterations occur early in life; (3) a predilection for certain vascular systems, such as the coronary, the abdominal aorta and the iliacs, exists and (4) the aging changes of the coronary tree are most commonly seen in the males.

Connective tissue is made up of ground substance, thick coarse bands of collagen, delicate elastic fibers and cellular elements consisting of fibroblasts, mast cells and histiocytes. The strength of connective tissue is derived from the high modulus of elasticity of the collagen fibers.

Collagen is formed by the arrangement of characteristic amino acids, particularly glycine,

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proline, and hydroxyproline, into a polypeptide strand by the fibroblast. Three polypeptide strands become laced into a spiral (which the physical chemists refer to as an alpha helix) and are held together by internal crosslinking.[4]

Because of the obvious importance of connective tissue (particularly the protein collagen) in the process of aging and because connective tissue is distributed in close association with muscles and joints, a technique by which connective tissue could be isolated from the remainder of the body was devised.[5] A plastic sponge was implanted in the subcutaneous tissue of the dorsum of laboratory animals, such as the rat, or along the left anterior chest wall of human volunteers. Through the interstices of the sponge, normal-appearing connective tissue developed. During the past four years, connective tissue obtained by sponge implantation has been studied in our laboratories and the following are some of the observations made.

Following the implantation of the sponge into rats, collagen is rapidly formed, appearing at the fifth to the seventh day, and increasing until the fourteenth to the twenty-first day. After twenty-one days of tissue growth, a sex difference in the amount of collagen was observed. In the female rat, the collagen content of the sponge twenty-one days after implantation was similar to that 300 days after implantation. The sponge implanted into the male animal continued to accumulate collagen even up to 300 days.[6] This difference could reflect the degree of metabolic inertness of collagen in the female or might indicate that the rates of synthesis and degradation of collagen equalled each other.

To determine the metabolic activity of collagen in the sponge-connective tissue of the rat, the rate at which lysine is converted to hydroxylysine was followed because hydroxylysine is a characteristic amino acid of collagen. It was evident that collagen obtained from the female rat was metabolically more active than that obtained from the male.[7] This suggested that in the female, collagen formation proceeded at a rate equal to collagen destruction whereas in the male, collagen formation occurred at a lower rate than in the female while collagen destruction proceeded at an even slower rate. Thus, the over-all effect was an increased collagen content in connective tissue obtained from the male but with no "net gain" of collagen in the sponge tissue from the female.

In addition to the variations in the rates of collagen formation and destruction, aging appears to influence the internal configuration of the collagen fiber as demonstrated by Baló and Banga[8] and by Verzár.[9] Rat tail collagen obtained from different-aged animals was exposed to a concentrated solution of potassium iodide and the contraction and relaxation of the fiber were followed. It was apparent that an accurate determination of animal age in months could be made by following the response of collagen to the solution of potassium iodide. "Young" collagen could be converted to "old" collagen by the exposure of the collagen fiber to dilute formalin solution. The effect of formalin on collagen is thought to occur by the addition of crosslinks between the three strands of polypeptides.[10]

Studies on the degree of acetic acid swelling of collagen obtained from Indians by sponge implantation indicated an apparent similar addition of crosslinks as a function of age. The swelling capacity decreases with age, and the effect of age is more apparent in the male than in the female donors.[11] The variation in swelling was interpreted to indicate a greater polymerization of the collagen in old than in young human volunteers.

To summarize the effects of age upon collagen: Fiber formation appears to be greater than fiber destruction, particularly in males. An increase in the strength and/or in the number of internal crosslinks of collagen occurs, that is, a form of accelerated polymerization.

Atherosclerosis

An atheroma appears to be a complication of the aging process. Some of the established facts concerning atheromatosis are:

(1) Endocrine
  (a) Predilection for males but occurs in females following the menopause
  (b) Accelerated by diabetes mellitus or oöphorectomy
(2) Vascular
  (a) Occurs in the intima
  (b) Patchy in character—localized at sites of bifurcation or sharp turns of a vessel
  (c) May be induced in a vessel as the result of the trauma of eddies or currents, that is, jet lesion
  (d) Appears to be accelerated by hypertension
(3) Metabolic
  (a) Increased lipids and elevated cholesterol concentration of the serum are associated with atherosclerosis in some patients

Considerable controversy has arisen concerning the morphogenesis of an atheroma. To examine the biochemical changes occurring in the aorta

with atheromatosis, the normal intima, intima containing an early atheroma and intima containing an advanced atheroma were studied.[12] No significant increase in cholesterol or lipid concentration was observed in the early atheroma. The advanced atheromatous area of the male contained no significant lipid elevations other than cholesterol, whereas in the female, other lipids (phospholipid and neutral fat) were also significantly increased. The significant biochemical changes noted consisted of an increase in certain amino acids, that is, glycine and hydroxyproline, which characterize collagen, and of the binding of hexosamine to the collagen of the intima. Thus, it appears that localized fibrogenesis of the intima preceded the lipid atheromatous lesion, a fact often suggested by the pathologists.

Fibroblasts synthesize cholesterol from a tagged two-carbon acetate molecule *in vitro*. The rate of cholesterol synthesis in rat connective tissue was greater in the male than in the female. Examination of the effects of pretreatment of the animal with various sex hormones revealed that estrogen enhanced the rate of cholesterol formation in the connective tissue obtained from the rat. The only hormone which depressed synthesis rate in both sexes was the hormone of pregnancy, relaxin. A dichotomy of response to sex hormones was observed between the connective tissue slices and the simultaneously incubated liver slices. The hormone which appeared to affect connective tissue and liver in a similar fashion was estrogen in the male rat.[13]

The effects of exogenous cholesterol upon rabbit connective tissue were followed. Multiple sponge implants were made and the biopsy-connective tissue was removed at various time periods. It was apparent that while the animal was on a high cholesterol diet increases in cholesterol (both total and esterified), total phospholipid and neutral fat of connective tissue occurred. Upon the cessation of the cholesterol diet and the return of the animal to a diet containing only trace amounts of cholesterol, the tissue phospholipids decreased as did the neutral fat. However, the cholesterol concentration of the connective tissue continued to rise. It was noted that at 170 days the serum cholesterol had returned to its control value while the tissue cholesterol had mounted to a concentration of almost 4 grams per cent. Thus, almost a twenty-fold reduction in serum cholesterol value failed to influence the cholesterol concentration of the sponge connective tissue.[14] Examination of the sponge-tissues from the cholesterol-fed animals indicated that the connective tissue had the appearance of an atheroma or a xanthoma.

Thus, it can be concluded that the fibroblasts synthesize cholesterol and that a large amount of exogenous cholesterol accumulates in young connective tissue. The localization of cholesterol in connective tissue is a subject of current investigation in our laboratory.

Summary

Aging produces changes in connective tissue, one of the principal tissues of the artery. These changes consist of a greater production than destruction of collagen, which results in an accumulation of collagen in the human male and postmenopausal female and in the male rat. Collagen obtained from old humans has apparently undergone a polymerization process with the addition of crosslinks between strands of the collagen polypeptide strands. At the site of vascular stress, localized fibrogenesis occurs with the formation of young connective tissue. New connective tissue, such as that obtained by sponge implant, not only synthesizes cholesterol but has a strong affinity for exogenous cholesterol.

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Observations on the Turnover of Cholesterol in a Human Subject

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THIS ARTICLE will be concerned principally with the routes of cholesterol excretion in man. Its justification is the emergence of new data which may require revision of some of our concepts on this subject.

Historical Considerations

Until recent years, the commonly held picture of cholesterol catabolism was as follows: Blood cholesterol is excreted through the wall of the intestine into the lumen. There, by the action of bacteria, it is converted to a greater or lesser extent into other substances, the chief of which is coprostanol. These degradation products, along with some unchanged cholesterol, are eliminated with the feces. In 1943, Bloch, Berg, and Rittenberg demonstrated the conversion of cholesterol to cholic acid in the dog.[1] Their experiments were not designed in a way to permit evaluation of the quantitative importance of the bile acids in cholesterol catabolism.

The picture was drastically altered when Chaikoff, Siperstein, and their co-workers[2,3] showed that in the rat, the bile acids are the most important end-products of cholesterol metabolism. More recently, Siperstein and Murray[4] carried out an isotopic experiment on a human subject with a temporary surgical bile fistula, and their results have been interpreted as evidence that the bile acid route is, quantitatively, the most important pathway in man, as well. This interpretation seems to have received rather wide acceptance. See, for example, a recent review[5] in which seventeen references are cited in support of it.

We have been reluctant to accept the bile acids as the principal medium for the excretion of cholesterol in man. Our hesitancy is based on two considerations: (1) We have been unable to detect in feces anywhere near the quantities of bile acids that would be expected from the turnover rate of cholesterol.[6] (2) Human feces, even with the subject eating a low sterol diet, contain large amounts of unsaponifiable, digitonin-precipitable material, the source of which is obscure if it does not represent excreted blood cholesterol.

Plan of the Experiment

The points mentioned above might possibly be reconciled if one were to assume that the bile acids are altered so drastically by the intestinal flora as to be unrecognizable in the stools, and, further, that the fecal coprostanol is derived largely from the intestinal mucosa, without prior mixing with the cholesterol pool of the blood. To test these hypotheses, the experiment described below was designed. The general plan was to inject cholesterol labeled with carbon 14 intravenously into a normal human being on a diet low in sterols, and then fractionate the radioactivity in the stools. If the fecal coprostanol is not derived from the blood, its specific activity should be much lower than that of the blood cholesterol. If large amounts of bile acids are excreted in altered condition, this fact should present itself in the form of a sizable amount of radioactivity falling neither in the digitonin-precipitable fraction nor in the known bile acids.

Materials and Methods

The subject was a fifty-two-year-old healthy man who was kept on a metabolic ward for the duration of the experiment. He was fed a formula diet which provided 2015 calories per day and consisted of skim milk 6 cups, whole milk 5 cups,

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sucrose 50 gms., chocolate syrup 100 gms. (protein 96.1 gms., carbohydrate 250.4 gms., fat 78.2 gms., cholesterol 169 mg.).

The cholesterol for injection was labeled at carbon 4, and was obtained from the Nuclear Instrument and Chemical Corporation. Its specific activity was 5μ/milligram. It was homogeneous by chromatography on silicic-acid-Supercel.[7] The dose to be given was dissolved in 4 ml. of 95 per cent ethanol, which was added to 35 ml. of isotonic sodium chloride solution. This mixture was administered intravenously during a period of about five minutes.

For determination of the specific activity of the serum cholesterol, free and total cholesterol were extracted and precipitated as the digitonide, as in the Schoenheimer-Sperry method,[8] except that all volumes were increased appropriately. Cholesterol was recovered from the digitonide by the method of Schoenheimer and Dam.[9] The recovered material was dissolved in 10 ml. of toluene containing 0.3 per cent 2,5-diphenyloxazole, and counted in a coincidence type liquid scintillation counter, with an efficiency of about 70 per cent. The amount of cholesterol counted was determined colorimetrically on a 1 ml. aliquot of the toluene solution, after evaporation to dryness. The Liebermann-Burchard reaction, as ordinarily carried out in the Abell method,[10] was used. The 3 mg. of fluor contained in the aliquot was found not to interfere.

Red cell cholesterol was isolated as follows: The packed cells were hydrolyzed for three hours in five times their volume of 15 per cent potassium hydroxide in 95 per cent ethanol. An amount of water equal in volume to that of the hydrolysate was added, and the mixture was extracted three times with twice its volume of petroleum ether (b.p. 36° – 60°). The petroleum ether was removed by distillation, and the specific activity of the cholesterol determined, as noted above.

For the recovery of labeled lipids from the feces, the specimen was weighed and mixed thoroughly, and an aliquot was extracted with boiling ethanol and petroleum ether, as previously described.[6] When the residue from this extraction was subjected to hydrolysis with alcoholic KOH and extraction with petroleum ether (as described above for red blood cells), less than 1 per cent of additional radioactivity could be removed. Counting of the dry residue itself as a check on the efficiency of the extraction was not very satisfactory because of the large mass involved, and the resulting low observable counting rate. An attempt to test the method in this way indicated that about 5 per cent of the radioactivity was unextracted, but this figure is undoubtedly too high because no correction could be applied to eliminate the counts from naturally occurring radioactive potassium.

Since one of the prime objects of the experiment was to make a balance sheet of the radioactivity in stools, aliquots of the crude alcohol extract were evaporated to dryness and counted, either as infinitely thin or infinitely thick plates. Additional aliquots were subjected to saponification and extraction as described above, and the unsaponifiable matter was plated for counting. The digitonin-preciptable fraction was also counted as the infinitely thick digitonide. Some of it was recovered from the digitonide, and aliquots were weighed and counted in the liquid scintillation counter, for direct comparison with the blood cholesterol. The infinitely thick samples were counted with a thin window Geiger-Mueller counter, but many of the thin samples were counted in a windowless flow counter. Although factors were worked out for the interconversion of results obtained in these various ways, all of the important comparisons were based on values obtained by identical techniques.

Fecal bile acids were extracted and isolated chromatographically as previously described,[6] except that in certain instances the residue from the ethanol extract was dissolved in 70 per cent aqueous ethanol and extracted repeatedly with petroleum ether (b.p. 60° to 70°), in order to provide a better initial separation of the bile acids from cholesterol, coprostanol, and other neutral sterols, which are not efficiently extracted from aqueous suspension.

The dimensions of the Celite columns used for the bile acid separations were 1.8 x 30 centimeters. The stationary phase was 70 per cent acetic acid, and elution was accomplished with 150 ml., 300 ml., and 450 ml. of petroleum ether containing 0, 40, and 60 per cent isopropyl ether, respectively. The eluate was collected in 200 tubes, each containing 4.5 milliliters. Aliquots from the tubes were placed on stainless steel planchets and the radioactivity counted in a gas flow counter. The remainder of the eluate in each tube was titrated with 0.015 N sodium hydroxide.

Methyl deoxycholate was prepared for liquid

scintillation counting by dissolving the deoxycholic acid eluted from the paper chromatogram, usually a quantity of about 0.5 mg., in 10 ml. of hot methanol containing HCl in a concentration of

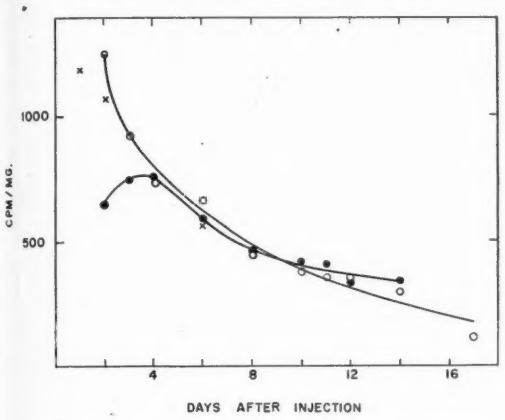

Fig. 1. Specific activity of blood cholesterol following intravenous injection of C^{14} labeled cholesterol.
○ Free cholesterol
● Esterified cholesterol
x Red cell cholesterol

0.28 N. The methanol-HCl solution was prepared by exposing the methanol to dry HCl gas.

Experimental

The subject was given 20 microcuries of C^{14}-labeled cholesterol intravenously. All stools were saved, and 20 ml. of blood were drawn daily. Figure 1 shows the decline in the specific activity of the free and esterified serum cholesterol, and of the red cell cholesterol. All of these fell quite close together during most of the experimental period. The specific activity of this pool declined by a factor of 2 between the fourth and tenth day following the injection.

Table I shows the weight of digitonin precipitable sterols isolated from the stools on the sixth, eighth, and tenth days after administration of the tracer, and a comparison of their specific activity with that of the total serum cholesterol on the same day. It is evident that the amount of endogenous sterols excreted by this patient was of the same order of magnitude as the values reported in the literature. Furthermore, the specific activity of these sterols corresponded to that of the blood a day or two earlier, providing proof that they came from the blood, without appreciable dilution from any other source.

Table II shows the distribution of radioactivity between unsaponifiable and bile acid fractions for the stool collected on the ninth day. Most of the cholesterol excretion products fell in the unsaponifiable fraction.

TABLE I. WEIGHTS OF DIGITONIN PRECIPITABLE STEROLS IN FECES, AND COMPARISON OF THEIR SPECIFIC ACTIVITY WITH THAT OF THE BLOOD CHOLESTEROL

	Days After Injection of Radioactive Cholesterol		
	6	8	10
Specific activity of total serum cholesterol, CPM/mg.	616	463	413
Specific activity of digitonin precipitable fecal sterols, CPM/mg.	665	583	462
Weight of sterols recovered from the digitonides, mg./day	621	976	635
Wet weight of stool, grams	79.7	128.0	80.9
Weight of aliquot extracted, grams	16.2	26.0	17.5
Weight of sterols actually counted, mg.	5.27	7.38	5.43

The counting was done in the liquid scintillation counter.

TABLE II. DISTRIBUTION OF RADIOACTIVITY BETWEEN UNSAPONIFIABLE AND BILE FRACTIONS FOR THE STOOL COLLECTED ON THE NINTH DAY

	Radioactivity in CPM	Per Cent of Total
Total ethanol extract	623,000	100
Unsaponifiable	450,000	72
Bile acid fractions	106,000	17
Unaccounted for	68,500	11

The counting was done in the windowless flow counter, at infinite thinness. Aliquots of several sizes were counted in each instance, to establish the fact that the counting rate was actually proportional to the size of the aliquot. The figure for the bile acids was obtained by adding the counts of the fractions which emerged from the column (Fig. 2). The nature of the compounds containing the radioactivity unaccounted for is unknown. They represent material which was not removed from the column with the solvents used.

TABLE III. RECOVERY OF UNSAPONIFIABLE MATTER FROM THE STOOL OF THE SEVENTH DAY

	Radioactivity in CPM	Per Cent of Total
Total ethanol extract	9500	100
Unsaponifiable	6700	70
Unsaponifiable, digitonin precipitable	5300	56

The counting was done with a thin window Geiger-Mueller counter, at infinite thickness, in dishes 2.5 cm. in diameter. The weight of material counted was always at least 140 mg., and the counts recorded above were corrected to the values that would have been obtained if all of the radioactivity present had been contained in a sample of that weight.

Table III shows the recovery from the stool of the seventh day, with the unsaponifiable matter divided further into fractions which did and did not precipitate with digitonin. Eighty per cent of the radioactivity in the unsaponifiable fraction was precipitable.

An example of the chromatographic distribution of radioactive and acidic compounds in the feces from the eighth day of the experiment is

shown in Figure 2. Deoxycholic acid (peak D) was further purified by paper chromatography[11] and eluted from the chromatogram with ethanol. The ultraviolet absorption spectrum of the product thus obtained was identical with that of pure deoxycholic acid. The concentration was determined from the absorption maximum at 385 μ. Radioactivity of the methylated material was measured in the liquid scintillation counter. The specific activity was 590 C.P.M./mg., compared with 463 C.P.M./mg. and 583 C.P.M./mg., respectively, for the serum and fecal digitonin precipitable sterols of the same day. The specific activity of the fecal deoxycholic acid of the seventh day was 620 C.P.M./milligrams.

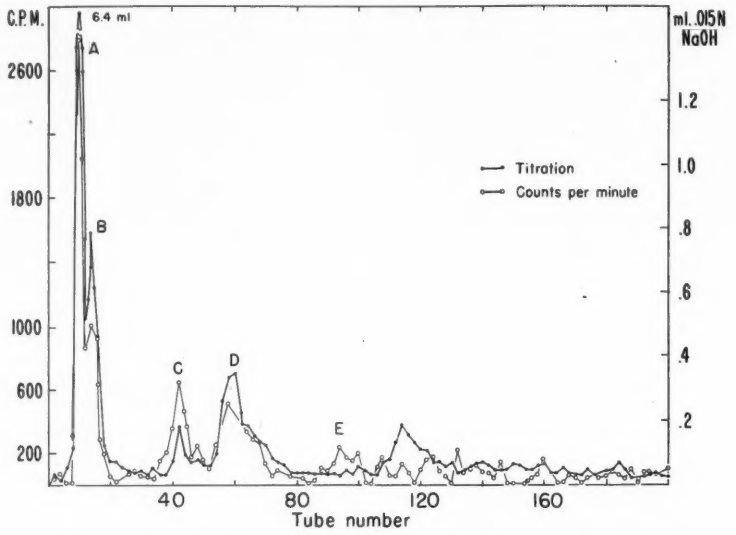

Fig. 2. Distribution of radioactive and acidic compounds in the bile acid fraction of feces eight days after the cholesterol-4-C^{14} intravenously.

A considerable amount of the radioactivity in peaks A and B (47 per cent) was found to result from a petroleum ether-soluble, digitonin-precipitable compound which was not removed by the initial separation. The remaining 53 per cent of the radioactivity was present as a non-digitonin-precipitable substance, soluble in alcohol. Some of the acidity in these peaks was non-radioactive fatty acid.

The amounts of deoxycholic acid excreted on the seventh and eighth days of the experiment were 24 mg. and 32 mg., respectively, accounting for less than 5 per cent of the total sterol excreted. The remainder of the bile acids had been sufficiently altered by intestinal flora so as to be no longer identifiable by the techniques used. It is quite probable that much of the radioactivity in the unaccounted-for category can be attributed to these altered bile acids or their derivatives.

Discussion

These results seem to indicate that in this individual, the bile acids played only a minor role in the excretion of cholesterol. An explanation is still required for the apparently opposite findings of Siperstein and Murray. Since both our conclusions and theirs are based on single experiments, individual variations may account for the discrepancies, and it is obvious that more work is needed. We wish to point out two features of their experiments, however, which may account for the differences:

(1) Their patient had a bile fistula, so that the normal reabsorption of bile acids was prevented. Under these circumstances, the turnover of bile acids might be expected to increase, and has, indeed, been shown to do so in the rat.[12] In their experiment, 39.6 per cent of the radioactivity administered was recovered in a period of fifty hours. We may calculate that the half-life of the body cholesterol with which the tracer was mixed was about sixty-eight hours, a much lower value than that commonly accepted for normal human subjects. Therefore, it appears likely that

the conversion of cholesterol to bile acids was accelerated under their experimental conditions.

(2) Their balance sheet of excreted radioactivity was based on a period of only fifty hours following administration of the tracer. Because of the time normally required for the passage of materials through the intestinal tract, a falsely low fraction of the radioactivity would be expected in stools collected during such a period.

An interesting conclusion may be drawn from the fact that the deoxycholic acid from our patient's stools had a specific activity approximating that of the serum cholesterol. Evidently, this deoxycholic acid was derived virtually entirely from cholesterol. No measurable quantity arose from unlabeled precursors, such as acetate, without going through the cholesterol pool.

Summary

(1) Carbon 14 labeled cholesterol was administered intravenously to a human subject on a diet low in sterols, and blood and stools were collected for a period of seventeen days.

(2) The stools were found to contain 0.5-1.0 gram of unsaponifiable, digitonin-precipitable material daily, the specific activity of which was equal to that of the blood cholesterol one or two days earlier.

(3) Fractionation of the radioactivity of the stools led to the following balance sheet: deoxycholic acid, 3 to 5 per cent; other compounds in the bile acid fraction, 13 per cent; unsaponifiable, 72 per cent, of which 80 per cent was precipitable with digitonin; unaccounted-for, 11 per cent.

(4) It was concluded that in our patient, the principal route of cholesterol excretion was the unsaponifiable fraction of the stools, with the bile acids playing a relatively minor rôle.

(5) The fecal deoxycholic acid was derived entirely from cholesterol.

Acknowledgments

The authors wish to thank Dr. B. J. Kennedy for his co-operation in making available the facilities of a metabolic ward and kitchen, and Mrs. Marion J. Franz, the dietitian in charge.

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(Continued from Page 156)

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Vasomotion in Systemic Arteries, Small Vessels and Veins Determined by Direct Resistance Measurements

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LITTLE ATTENTION has been given the possibility that macroscopic vessels might contribute significantly to the maintenance and adjustability of resistance to blood flow across systemic vascular beds. These functions have been mainly attributed to the arteriol. Arteries and veins are relatively abundantly supplied with smooth muscle and autonomic nerve connections. When surgically exposed, they respond to various local physical and chemical stimuli with intense constriction. Despite this demonstrated potential, the details of their behavior under usual conditions are poorly understood. The obvious importance of artery and especially vein caliber changes to blood volume distribution, cardiac filling and water and salt transport across capillary membranes seemed to justify a detailed study of small and large vessel resistance responses to various stimuli. Partial findings of this study follow.

Methods

The methods employed were developed in Dr. M. B. Visscher's laboratory at the University of Minnesota and subsequently refined at the Northwestern affiliated V.A. Research Hospital in Chicago and at the Army Medical Research Laboratory at Fort Knox, Kentucky. Dr. Visscher suggested the study in 1951 and many of the ideas eventually incorporated into it were originally his.

Artery, vein and small vessel caliber changes in the foreleg of the anesthetized dog were inferred from resistance values calculated from directly measured levels of pressure and flow rate (Fig. 1). Foreleg blood flow rate was either controlled with a blood pump* or measured with a flow meter** interposed in the brachial artery. Pressures were measured at four sites along the length of the bed. These sites included the brachial artery just distal to the pump or flow meter, a foot pad small artery, a dorsal subcutaneous paw small vein and the cephalic vein at about the level of the elbow. Pressure gradients from brachial artery to cephalic vein, brachial artery to small artery, small artery to small vein and small vein to cephalic vein were calculated. Resistance values for the entire bed, arteries, small vessels (arteriol, capillary, venule) and veins were separately derived by dividing the respective gradients by the blood flow rate.

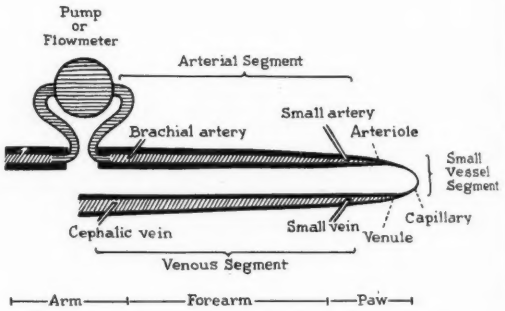

Fig. 1. Schematic drawing showing experimental arrangement for measurement of resistance to blood flow in arteries, small vessels and veins of dog foreleg.

Pressures were measured in the small artery and vein by entering 1 mm. sized vessels with 0.5 mm. glass or stiff plastic catheters† and threading them distally as far as possible (Fig. 2). The catheters, about 6 cm. in length, were advanced 4 to 5 cm. peripherally. It was necessary to manipulate the tip through valves in the case of the vein. The

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*Sigmamotor Pump Model T-6, Sigmamotor, Inc., Middleport, N. Y.

**Rotometer and Recording Unit No. 45, Clifford Wilson, 325 West 42nd Street, Indianapolis 8, Indiana.

†Albert E. Afford, Williams Ave., Barrington, N. J.

1 mm. vessels were entered either following surgical exposure or by needle puncture through the intact skin. In the latter case, a 21 thin walled needle‡ was directed peripherally and the

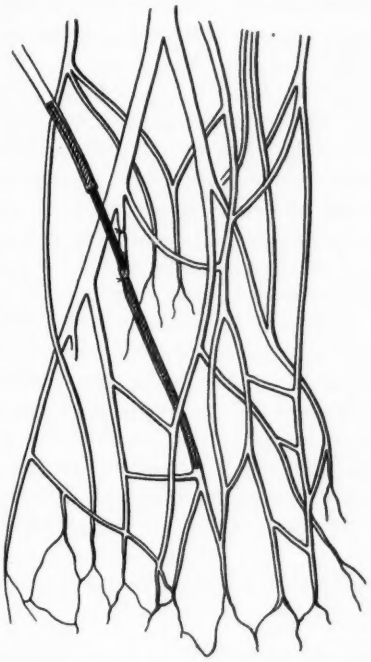

Fig. 2. Method used for measurement of pressure in dorsal limb subcutaneous small veins. Catheter completely occludes lumen of 0.5 mm. vein and pressure recorded is then that in distal collaterals. Vessel surgically exposed only at point of entrance of catheter and tied proximally. Catheter manipulated in retrograde direction 4 to 5 cm. Catheter may also be inserted through intact skin utilizing special thin wall needles. Same method employed for measurement of small artery pressure.

catheter passed through it. The needle was then withdrawn. Since in their final positions the catheter tips completely occluded the vessel, the intraluminal pressures recorded§ were then those in distal collateral vessels. Small and large vein pressures were also studied in trained wakened dogs under local anesthesia and in wakened humans. Detailed descriptions of the methods employed have been published previously.[1,2]

Results

General Anesthesia

General Considerations.—Small vein pressure exhibits cardiac and respiratory variations which resemble those in large systemic arteries.[1] The waves are not affected by venous compression but disappear upon arterial occlusion suggesting that they are transmitted from the arterial side. Though

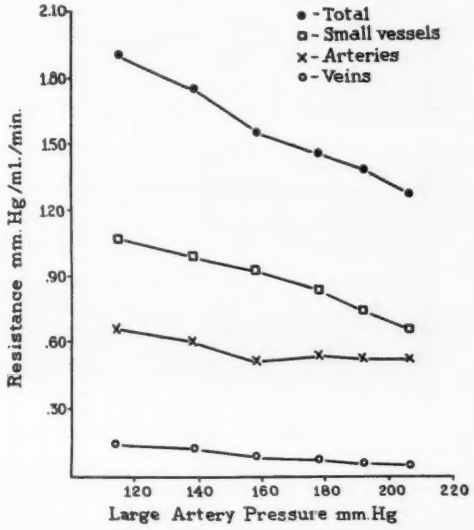

Fig. 3. Relation of total and segmental foreleg vascular resistances to brachial artery pressure. Anesthetized animal. Changes induced by varying foreleg blood flow rate with a pump inserted high in brachial artery. Extreme flow rates 56 and 163 ml./min. The values for small artery, small vein and large vein pressures at these flow rates were 75 and 125, 15 and 16, and 6 and 7 mm. Hg., respectively. Resistance variations represent homogeneous passive changes resulting from change of transmural pressure.

the mean pressure in a given vein remains quite constant with time it ranges from 8 to 28 mm. Hg. between different veins. This interindividual variation in pressure level likely is related to differences in venous resistance, blood flow rate and size of vessel catheterized between forelegs. The average small vein pressure value is about 14 mm. Hg. and this is to be compared to that of 4 mm. Hg. for the cephalic vein in the same leg. A positive small to large vein pressure gradient is always present. Foot pad small artery pressure averages about 75 mm. Hg. This level also varies from vessel to vessel likely for reasons similar to those listed for small vein pressure.

Homogeneous Passive Resistance Changes.—Figure 3 shows that elevation of vessel pressures by varying blood flow rate with the brachial artery pump is associated with resistance decreases in all segments.[2] That the resistance variations likely represent changes in caliber is indicated by

‡Bishop Blue Label Hypodermic Needles, J. Bishop and Co. Platinum Works, Malvern, Penna.

§Any manometer with a volume displacement of 0.05 mm.^{3}/100 mm. Hg. or less is adequate.

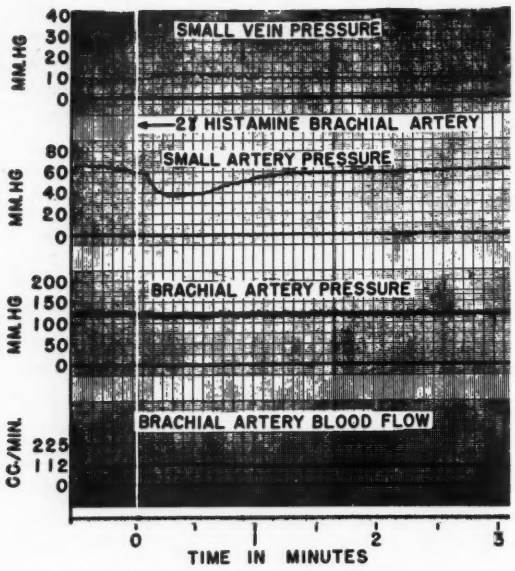

Fig. 4. Effect of histamine phosphate upon brachial artery, small artery and small vein pressure and blood flow rate in foreleg of pentobarbitalized dog. Flow rate measured with flowmeter interposed high in brachial artery. Histamine injected instantaneously into brachial artery just distal to flowmeter. Cephalic vein pressure, not shown here, did not change.

Homogeneous Active Resistance Changes.—Small brachial artery doses of acetylcholine, acetyl beta metha choline, histamine, aminophylline, papaverine, ethyl alcohol, hexamethonium, pitocin and priscoline greatly decrease small artery pressure, slightly increase small vein pressure and increase blood flow rate (Figs. 4 and 5). Brachial artery and cephalic vein pressures do not change.[3,4] One of these, acetylcholine, has been studied in detail (Fig. 6). Blood flow rate was maintained constant with the pump while acetyl choline was constantly infused into the brachial artery. Under these conditions large artery, small artery and small vein pressures fall. Calculated resistance decreases in each segment. The active nature of the caliber increases is established by the fact that they occur in the presence of falling intraluminal pressures. This same response is usually observed in the rewarming period following cold exposure. Denervation also actively dilates the small vessel segment. The addition of intra-arterial phentolamine induces further active small vessel dilatation and sometimes active artery dilatation.

Intra-arterial injections of commercial epineph-

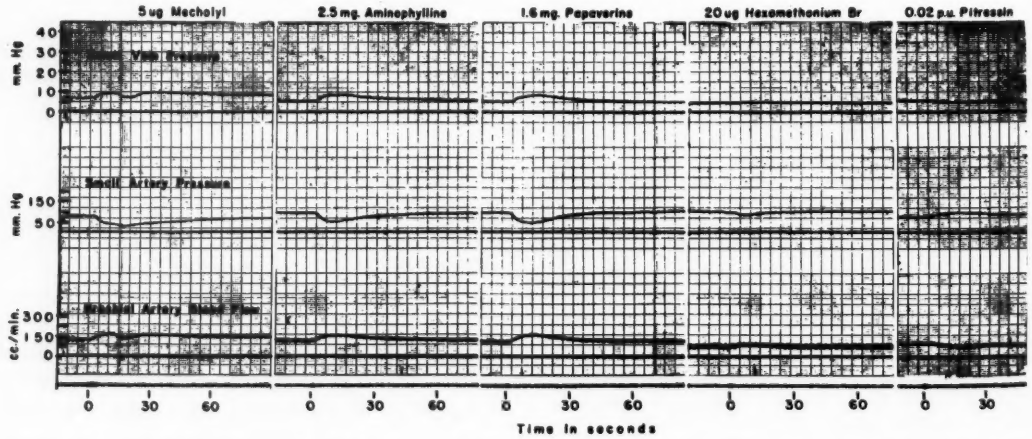

Fig. 5. Effect of instantaneous brachial artery injection of various substances upon foreleg blood flow rate and small vessel pressures. Brachial artery and cephalic vein pressures did not change significantly.

the fact that the variations are greater than might be expected from dynamic changes in viscosity alone. Resistances decrease because intraluminal and hence, transmural pressures increase, thereby passively increasing vessel calibers. On the other hand, lowering pressures by decreasing blood flow rate results in a resistance increase in each segment due to passive constriction.

rine, l-epinephrine (Fig. 7) and l-norepinephrine cause large increases of small artery and vein pressures. Blood flow rate decreases and large artery and vein pressures remain unchanged. Pitressin, angiotonin and ergotamine cause the same changes except that small vein pressure remains unchanged or falls slightly (Fig. 5). Commercial epinephrine and l-norepinephrine

have been studied[5] when administered by constant infusion with blood flow rate maintained constant (Fig. 8). Norepinephrine elevates brachial artery, small artery and small vein pressures. Resistance increases in each segment. Attesting to the active nature of the caliber decreases is the fact that all calibers decrease in the presence of increasing intraluminal pressures. This same response usually

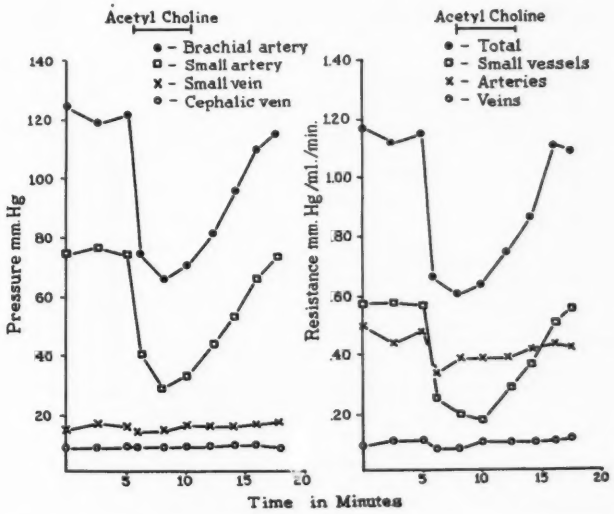

Fig. 6. Effect of acetylcholine upon vascular pressures and segmental vascular resistances in foreleg of pentobarbitalized dog. Blood flow rate maintained constant at 100 ml./min. with blood pump interposed high in brachial artery. Acetylcholine constantly infused into brachial artery just distal to pump at rate of 30 γ/min. Resistance changes represent homogeneous active dilatation.

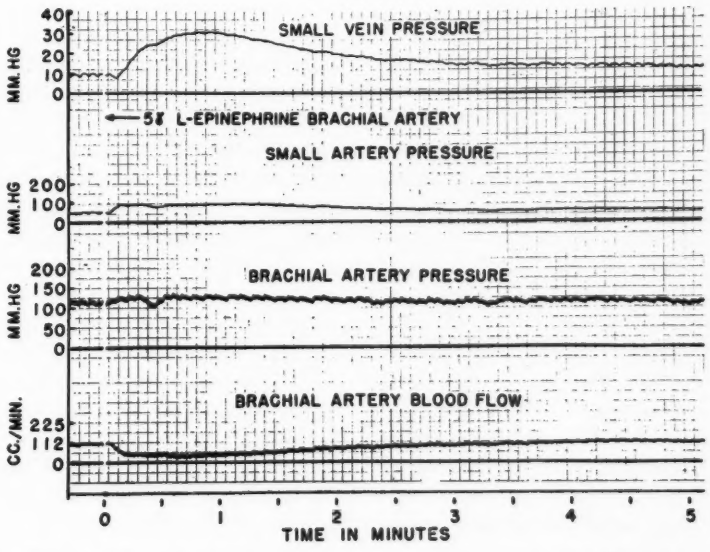

Fig. 7. Effect of instantaneous brachial artery injection of l-epinephrine bitartrate upon small and large vessel pressures and blood flow rate in foreleg of pentobarbitalized dog. Cephalic vein pressure did not change.

occurs during cold exposure. Bilateral vagotomy also regularly causes active small vessel constriction associated with less regular active artery constriction.

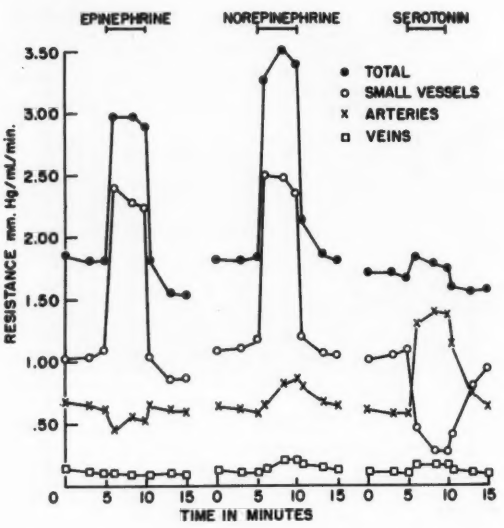

Fig. 8. Average effect of epinephrine, norepinephrine and serotonin upon total and segmental vascular resistances in eleven dog forelegs. Foreleg blood flow rates maintained constant at average values of 69, 69 and 75 ml./min., respectively. Epinephrine hydrochloride, l-norepinephrine bitartrate monohydrate and serotonin creatinine sulfate infused into brachial artery at rates of 5, 5 and 10 γ/min., respectively. Norepinephrine changes illustrate homogeneous active constriction, epinephrine active small vessel constriction concomitant with passive artery dilatation and serotonin active artery and vein constriction concomitant with active small vessel dilatation.

Combinations of Active and Passive Resistance Changes.—The epinephrine response with blood flow rate maintained constant illustrates active small vessel constriction concomitant with passive artery dilatation (Fig. 8). The artery segment dilated because its average intraluminal pressure increased 75 mm. Hg. The dilatation is less, however, than would be expected from the pressure change alone[2] indicating that epinephrine also tends to constrict arteries.[5] A similar combination of directionally opposite active and passive segmental changes occurs following venous obstruction.[2] This maneuver, when carried out with blood flow rate constant, is usually associated with active small vessel constriction and passive artery and vein dilatation (Fig. 9). Since pressures increase in all vessels, the small vessel constriction is active in nature whereas the dilatation in arteries and veins is passive. The small vessel constrictor response can be converted to a dilator response by destroying nerve function in the limb. The response has been called the 'veni-vasomotor'

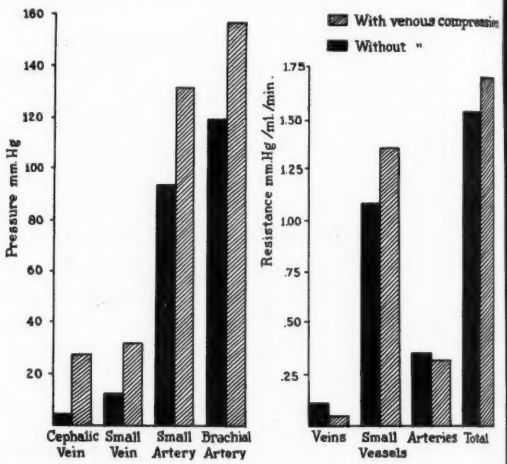

Fig. 9. Effect of venous obstruction upon vessel pressures and segmental vascular resistances in foreleg of pentobarbitalized dog. Blood flow rate maintained constant at 75 ml./min. Venous obstruction accomplished by tightening a tourniquet high on the leg. Response illustrates passive vein and artery dilatation concomitant with active small vessel constriction.

reflex by Burton's group[6-10] and the 'venous-arteriolar' reflex by Haddy and Gilbert.[2,11]

Heterogeneous Active Resistance Changes.—Directionally opposite active changes in various segments were an unexpected finding. During cold exposure, all segments usually constrict.[12] Upon return to room temperature, the small vessel segment immediately begins to dilate. However, this is not always true of the vein and artery segments. In some instances the veins continue to actively constrict during the rewarming period at a time when small vessels actively dilate. Kelly and Visscher[13] have reported changes which likely represent the same event following the release from faradic sympathetic nerve stimulation. The cold-induced venous constrictions are associated with high levels of small vein pressure. Using these catheterization techniques in humans, Stead and Wallace[14] have reported small vein pressures as high as 40 to 50 mm. Hg. during cold exposure. Active artery constriction also occasionally occurs during the rewarming period concomitant with active small vessel dilatation (Fig. 10). Active artery dilatation concomitant with small vessel

constriction is observed in nerve intact forelegs if CO_2 tension and H^+ concentration are decreased by hyperventilation.[15] Since the two responses are directionally opposite and of approximately equal magnitude, total resistance does not change significantly. On the other hand, the opposite changes are observed when H^+ concentration and CO_2 tension are increased by ventilation with 20 per cent CO_2.

The most striking example of directionally opposite active changes in segmental resistances yet observed is that associated with local serotonin administration.[5] Figure 11 shows that intra-arterial injection of this substance results in little change in flow rate and large artery pressure but a large decrease in small artery pressure associated with an increase in small vein pressure. Large vein pressure does not change. Resistance calculations (Fig. 8) show a striking increase in artery resistance and a decrease in small vessel resistance. Venous resistance also increases and in some instances is associated with small vein pressure levels as high as 35 mm. Hg. The over-all result is little change in total resistance. An examination of the direction of pressure changes in the various segments indicates that all the caliber changes are active in nature. These findings may explain how serotonin produces peculiar skin color changes without predictable blood pressure changes when injected into intact animals or man.

Numerous investigators have noted that administration of serotonin produces unpredictable changes in systemic arterial blood pressure. Page and McCubbin[16] observed that the direction of change seemed to be related to the pre-existing level of resistance in the system. The present studies[17] offer an explanation for their finding. In the experiment illustrated in Figure 12, administration of serotonin decreased total resistance when nerves were intact and control total resistance high. Following nerve section, control total resistance decreased because of small vessel dilatation. In the latter low resistance preparation, administration of serotonin increased total resistance because the small vessels, being maximally dilated already, could not further dilate in order to offset constriction in arteries and veins. In a series of experiments recently completed, four levels of small vessel resistance were studied in the same animal. The magnitude of serotonin-induced small vessel dilatation was directly related to the pre-existing level of small vessel resistance.

Local Anesthesia

Experiments in trained unanesthetized animals suggest that a number of the above events may occur spontaneously in normal animals or may be

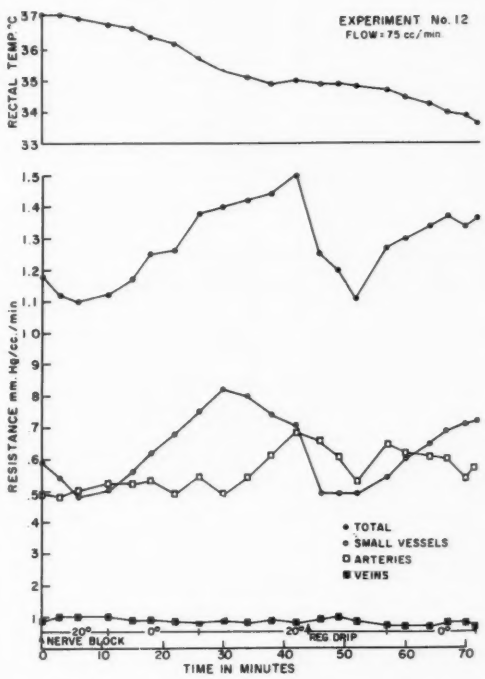

Fig. 10. Unusual effect of cold exposure upon total and segmental vascular resistances in foreleg of pentobarbitalized dog. Foreleg blood flow rate maintained constant at 75 ml./min. Entire transverse diameter of foreleg blocked with 2 per cent procaine at level of elbow at point indicated. O° C exposures accomplished by placing animal in cold room for periods indicated. Phentolamine methanesulfonate infused into brachial artery at rate of 600 γ/min. from forty-third to seventy-second minute. Experiment illustrates active artery constriction concomitant with active small vessel dilatation resulting in continued rise in total resistance during first rewarming period.

precipitated by certain pathological conditions. Average, small and large vein pressures in unanesthetized animals are not greatly different from those under general anesthesia.[1] The respiratory waves are not so readily apparent since the ventilatory cycle is more rapid and less regular. However, if small vein pressure is observed over a long time period in wakened animals, it sometimes spontaneously fluctuates over wide ranges in the absence of significant changes in large vein pressure.[1]

Studies have also been made in seventeen unanesthetized dogs with artificially-produced pul-

monary stenosis and tricuspid insufficiency.[3,18] Eight were compensated and nine were decompensated at the time of study. The independent variability of small vein pressure was even more apparent in these animals than in those with normal circulatory systems. The gradient from small to large vein, integrated over long time periods, was 11.3 mm. Hg. and is to be compared

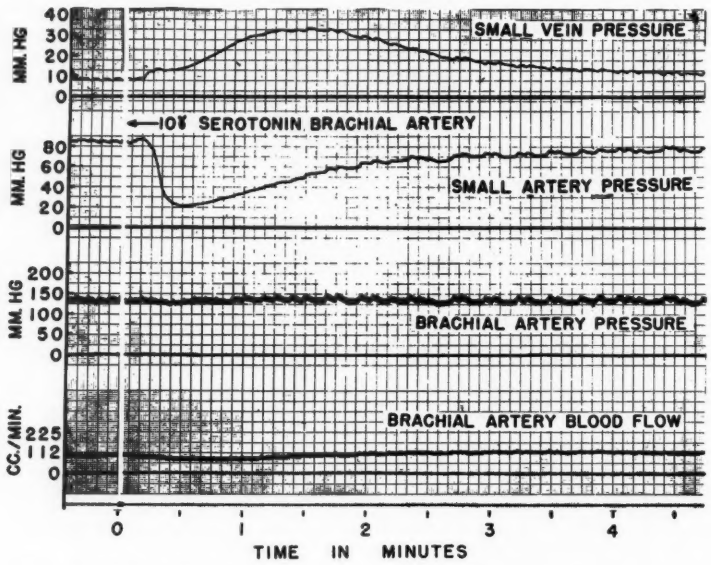

Fig. 11. Effect of serotonin creatinine sulfate upon vascular pressures and blood flow rate in foreleg of pentobarbitalized dog. Instantaneous injection made just distal to branchial artery flowmeter. Cephalic vein pressure did not change significantly.

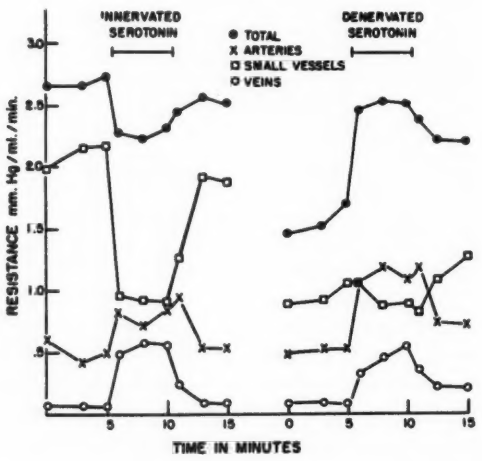

Fig. 12. Effect of nerve section upon total and segmental vascular resistance responses to serotonin in foreleg of pentobarbitalized dog. Blood flow rate maintained constant at 50 ml./minute. Serotonin creatinine sulfate infused into brachial artery just distal to blood pump at rate of 10 γ/min. Experiments executed immediately before and after cutting all nerves high in the foreleg. Experiment illustrates the mechanism whereby serotonin induced total resistance decrease in a high resistance foreleg is converted to a total resistance increase in a low resistance foreleg.

to a value of 6.0 mm. Hg. from a group of normal wakened animals. Figure 13 shows that exercise also elevates the gradient from small to large vein in normal animals.[1] Elevated venous gradients were also observed in four edematous extremities. In one case, the measurements were made in a wakened dog with edema due to cardiac decompensation produced by artificially-induced mitral stenosis.[3] The three others were under general anesthesia and the hindleg edema was the result of chronic iliac and femoral arteriovenous fistulae.[1]

Gradient changes may arise from variation in blood flow rate or resistance. Since the animals were awake, flow rates are not available. However, large changes in flow rate produce minimal variation of small and large vein pressures in anesthetized animals (Fig. 3).[2] This suggests that the above-mentioned pressure and gradient changes in the venous segment of wakened animals are truly due to active venomotion.

A study of the venous system of humans is in progress. Simultaneous measurements have been made of pressures in the antecubital vein and a subcutaneous small vein at the base of the fingers

in the same extremity. The catheter is introduced into both veins through needles inserted through the intact skin. In ten normal subjects, the values for small and large vein pressure average 11.6 and 8.0 mm. Hg., respectively. To date, the large spontaneous fluctuations of small vein pressure mentioned above have not been observed in humans. It should be noted, however, that it has not always been possible to advance the catheter as far distally in the human as in the dog.

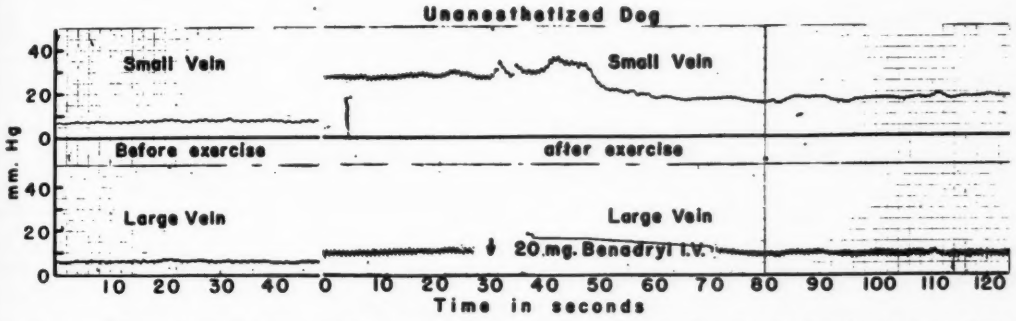

Fig. 13. Effect of exercise upon small and cephalic vein pressures in foreleg of trained wakened dog. Catheters inserted under local procaine anesthesia. Animal lying on side during period pressures were recorded. Recordings immediately before and after animal was made to run 150 yards at the approximate rate of 5 miles/hr. Catheters were disconnected from strain gauges, filled with a saline-heparin solution, tightly stoppered and taped to animal's leg without disturbing their positions in the veins for the period of exercise. Drug injection into cephalic vein catheter during period indicated.

Discussion

These observations indicate that macroscopic arteries and veins may contribute significantly to the maintenance and adjustability of resistance to blood flow in dog limbs. Further, they suggest that arteries, small vessels, and veins are independent resistances. Their magnitudes may actively or passively change in the same or opposite direction.

These statements are perhaps best illustrated by serotonin administration. Serotonin appears to shift the major portion of total resistance from small vessels to arteries and veins. The segmental changes are large and of opposite direction.

Bore changes in various segments are important for two reasons. They vary volume distribution of blood within these segments. Changes in venous volume are especially important because they directly influence the rate of cardiac filling and thereby, the cardiac output. Bore changes also result in pressure variations which, in turn, may influence the transport of water and electrolytes across capillary membranes. Active venous constriction was associated with small vein pressures as high as 50 mm. Hg. in some instances. Since capillary pressures in open beds cannot be lower than small vein pressure, net transport of fluid was likely out of the capillary in these instances. Therefore, further knowledge about venous resistance and small vein pressure changes may shed light upon the mechanism of edema production and tissue water storage, in general. Changes in artery caliber likely do not influence blood volume distribution as acutely as do variations in venous caliber. They do, however, greatly influence capillary pressure and the direction of change is the same as that caused by changes in arteriolar caliber.

These studies emphasize another rather practical point. Since veins can actively constrict and dilate, there need be no fixed correlation between small vein pressures and those in larger, more central veins. Reliance upon large vein pressure changes to indicate what is going on at the periphery is, therefore, obviously improper. The same applies to the arterial side of the circuit.

Conclusions

Methods are described for measurement of resistance in arteries, small vessels and veins of the dog foreleg. Observations under various circumstances indicate that these vessel segments constitute independent resistances whose magnitudes may vary in the same or opposite directions through both active and passive mechanisms. Veins and arteries of greater than microscopic size may, under certain conditions, contribute greatly to the maintenance and adjustability of resistance to blood flow across systemic vascular beds.

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DIET, PHYSICAL ACTIVITY AND THE SERUM CHOLESTEROL CONCENTRATION

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Experimental Cerebrovascular Disease

A Review

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RELATIVELY few studies of experimental cerebrovascular disease in animals have been recorded. These studies have tended to lag behind clinical and pathologico-anatomic investigations and too frequently have served as confirmatory work after clinical impressions have been virtually accepted.

It is obvious that investigation with laboratory animals cannot be related directly to human disease. No animal has a cerebral vascular supply entirely comparable to that of man, and most, if not all, animals have a considerably greater cerebral circulatory reserve. For example, my associates and I[1] have learned that 50 per cent of dogs which have had both vertebral arteries, both common carotid arteries and all their terminal branches ligated in the neck simultaneously will survive and recover near normal function. Another point regarding the limitations of these studies is that young animals ordinarily are used; seldom, if ever, do these animals have diseased cerebral blood vessels. It is possible to use dogs in which atherosclerosis has been produced by thiouracil and high-cholesterol diets. However, even when rather pronounced changes have occurred in many arteries of the dog's body, the change in the cerebral vessels has been little or none.[2]

Production of Experimental Cerebral Infarction

My colleagues and I have been interested in satisfactory methods for the production of infarcts in order that we might determine how these infarcts can be altered by various procedures or drugs. Ligation of individual arteries in the neck rarely causes focal infarction in animals. Craniotomy followed by occlusion of individual cerebral arteries has been performed in a number of studies. In a high percentage of instances, occlusion of the middle cerebral artery with a clip in dogs or monkeys has produced hemispheric infarction, but with considerable variation in size, which is one of the difficulties in interpretation of data, regardless of the method used for producing the infarcts.

A number of different foreign substances, including various seeds, sand, air, iron filings and stainless-steel ball bearings, have been injected into the arteries of the neck in animals. These methods have met with varying success in producing lateralized focal infarction of any predictable nature. Denny-Brown and associates[3] produced hemorrhagic cerebral infarction by abruptly distending a cerebral vein with an isotonic solution of sodium chloride, the infarct occurring in the area drained by that vein.

Effects of Other Factors on Experimental Cerebral Infarcts

Rosomoff and Holaday[4] noted that hypothermia in dogs reduced the cerebral blood flow an average of 6.7 per cent of the control flow per degree when the temperature was reduced from 35° to 25° C. Cerebral consumption of oxygen was reduced correspondingly. Rosomoff[5] found that dogs in which clips were placed to occlude the middle cerebral artery had much smaller infarcts and many fewer clinical signs when they were under hypothermia than did control normothermic dogs.

Hypotension induced by drugs or by bleeding has been found in several studies to affect adversely the size of cerebral infarcts in cats, dogs and monkeys after a clip has been placed to occlude the middle cerebral artery.

Meyer and co-workers[6] measured the availability of oxygen in various zones of cerebral infarcts in cats and monkeys by the use of an electropolarograph. They noted in unstable parts of the infarcts that the available oxygen passively fol-

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lowed decreases in the blood pressure, and they concluded that maintenance of blood pressure at optimal levels was the most important factor in maintaining the available anastomotic circulation. They also noted that the pattern and speed of recovery of the infarcts were not affected by cervical sympathectomy, stellate ganglionectomy, sectioning the seventh cranial nerve and breathing 5 per cent carbon dioxide and 95 per cent oxygen.

Corday and associates[7] reported more pronounced electroencephalographic changes in the homolateral hemisphere when monkeys with one internal carotid artery partially or completely occluded were subjected to hypotension; these changes were reversed readily when the blood pressure was restored to normal.

Hypertension induced by drugs after the production of cerebral infarcts in dogs increases the extent of hemorrhagic infarction.

Production of Hemorrhagic Infarction

Hain and co-workers[8] concluded that they could produce hemorrhagic infarcts in dogs by occluding the middle cerebral artery proximal to the origin of the perforating branches. They obtained pale infarcts when the occlusion was distal to these branches. It was thought that collateral circulation from these branches was the origin of the hemorrhagic character of the infarcts and that the blood was present by virtue of diapedesis before necrosis of the blood vessels occurred.

Globus and associates[9] produced infarcts by occluding the middle cerebral artery in dogs. After varying periods of delay, phenylephrine (neosynephrine) hydrochloride was given intravenously on several occasions, thus producing fresh focal hemorrhages in two-thirds of the dogs. Although hemorrhagic infarction and frank hemorrhage were not clearly differentiated in their study, the photographs revealed that frank hemorrhage occurred on several occasions, and intraventricular hemorrhage was present in one dog in which the infarct was thirty days old.

Fazio and Sacchi[10] induced infarcts in dogs by air emboli and thought that hemorrhagic infarction was increased by the delayed intravenous administration of epinephrine (adrenalin). They concluded that infarction was increased further by venous stasis produced by a head-down position plus compression of the jugular veins.

Harvey and Rasmussen[11] produced hemorrhagic cerebral infarcts in monkeys by complete occlusion of the middle cerebral artery for fifty minutes. This, in effect, is re-establishment of the circulation through damaged tissue. Welch,[12] in his classic study of hemorrhagic infarction of the small intestine of the dog in 1887, produced severely hemorrhagic infarction when all collateral channels had been previously excluded, and he then incompletely occluded, for a prolonged period, the superior mesenteric artery so that the blood barely flowed. I am not aware that a similar study has been performed in regard to the cerebral circulation.

Other Experimental Cerebrovascular Diseases

Hypertensive encephalopathy was produced in rats by Byrom.[13] The hypertension was effected by excising one kidney and constricting the opposite renal artery. The encephalopathic symptoms were relieved promptly by abolition of the hypertension. Organic lesions were found in 55 per cent of the rats at necropsy; these consisted of focal arterial necrosis, small infarcts and arterial or capillary hemorrhages. Diffuse spasm in small arteries and diffuse and focal spasm in larger arteries were noted in these rats by observing the brain through a cranial window. Byrom concluded that the encephalopathy and arterial necrosis both resulted from arterial spasm.

Experimental cerebral arterial aneurysms have received little attention. McCune and associates[14] produced aortic aneurysms in dogs by injecting nitrogen mustard under the adventitia. Similar procedures have been directed toward the carotid artery in the neck, but aneurysms have not been consistently produced in the vessels of the neck or the intracranial arteries.

Cerebral Infarction and Anticoagulant Therapy

My associates and I have found two useful methods for the production of cerebral infarction. The first method[15] involves the introduction of 0.2 to 0.3 ml. of liquid vinyl acetate into one internal carotid artery of dogs; this material promptly hardens on contact with the blood and occludes the internal carotid artery, usually the middle cerebral artery and sometimes other cerebral arteries. The material usually is in a continuous strand within the arterial tree. The other method[16,17] involves similar injection of approximately the same amount of a forty-eight-hour-old homologous blood clot. The obstruction in this technique should be thought of as a shower of

emboli consisting of fragments of clot that lodge in positions such as the trifurcation of the middle cerebral artery. The age of the clot (forty-eight hours) is an important consideration in this technique.

TABLE I. EXTENT OF HEMORRHAGE IN CEREBRAL INFARCTS PRODUCED BY VINYL ACETATE AND BY CLOTS

Hemorrhage, Per Cent	Vinyl Acetate		Homologous Clot	
	Number	Per Cent	Number	Per Cent
0-30	13	93	2	11
31-60	0	0	4	22
61-90	0	0	4	22
91-100	1	7	8	45

Both these methods have yielded lateralized cerebral infarcts in approximately 75 per cent of the animals. This figure represents those infarcts large enough to be readily detected clinically, which means that the animal has hemiparesis or forced circling or both. Of the dogs so affected, about half fail to survive the first two days after the infarct is produced, which limits the value somewhat. The other half of this group survive indefinitely and recover to varying degrees.

One of the difficult problems in such studies is to convey to other persons the extent of an infarct and its hemorrhagic nature without detailed description. Because of this, we have made a practice of cutting each brain into seven standard coronal sections, and a scale drawing on a printed form has been made, representing structures in each of these standard sections. The infarcts then are outlined on the printed sheets, the hemorrhagic zones being noted in red and the nonhemorrhagic parts in blue. These areas then can be traced with a planimeter, which gives the total area of infarction in the seven sections. Thus, the complexities of an infarct can be reduced to numbers, which can be used for comparison. It is not possible to indicate satisfactorily the density of these areas. The limitations are obvious, but the technique has proved useful.

Practically all the infarcts produced by vinyl acetate were less than 30 per cent hemorrhagic (Table I). The one extremely hemorrhagic lesion was an exception to the relatively unaltered infarcts produced by this method. An earlier group of seventeen infarcts produced by vinyl acetate further support this experience. On the other hand, the infarcts produced by injection of clots varied in the amount of hemorrhage, but two-thirds were more than 60 per cent hemorrhagic (Table I).

Alteration of Infarcts by Anticoagulants.—Since anticoagulants have had such increasing clinical use in the last few years in cerebrovascular diseases, my colleagues and I have conducted several studies aimed toward increasing our knowledge about alterations of experimental cerebral infarcts by these agents. We were interested in whether cerebral infarcts had a more hemorrhagic character when anticoagulants were given immediately after the infarct was produced. Since many infarcts are strikingly hemorrhagic without anticoagulants and since such great variability occurs in this feature, one must depend on the over-all picture in a number of animals to obtain any useful data.

TABLE II. EFFECT OF ANTICOAGULANTS ON EXTENT OF HEMORRHAGE IN CEREBRAL INFARCTS PRODUCED BY VINYL ACETATE

Hemorrhage, Per Cent	Control Dogs		Dogs Given Anticoagulants	
	Number	Per Cent	Number	Per Cent
0-30	13	93	16	64
31-60	0	0	8	32
61-90	0	0	1	4
91-100	1	7	0	0

When ethyl biscoumacetate (tromexan) and bishydroxycoumarin (dicumarol) are given, it requires a little more than twenty-four hours to reduce the prothrombin activity in dogs to the therapeutic range. Our initial experience[18] involved thirteen animals which were given anticoagulants on the same day the infarct was produced and survived at least thirty hours, allowing the anticoagulants to become effective. These infarcts were produced with vinyl acetate, which, as already noted, usually produces relatively nonhemorrhagic lesions. Eleven of these infarcts were strikingly hemorrhagic when compared to the lesions in thirteen control dogs which also survived at least thirty hours but did not receive anticoagulants. A considerable range of hemorrhagic infarction often was noted even within the same infarct. In four animals, the entire infarct was occupied by hemorrhage, and the same condition plus intraventricular hemorrhage was noted in a fifth dog. The prothrombin activity in this group of animals was made excessively low intentionally, the average of the lowest values for each animal

being 5 per cent of the normal prothrombin activity.

We[19] then conducted a similar study, taking special care to maintain the prothrombin activity at approximately 15 to 30 per cent of normal.

TABLE III. EFFECT OF ANTICOAGULANTS ON SIZE OF INFARCTS PRODUCED BY CLOTS

Infarct, Per Cent	Control Dogs	Dogs Given Anticoagulants
0-3	5	8
4-7	3	5
8-16	5	1
16+	1	0

This study was limited to dogs which survived at least forty-eight hours, so that full anticoagulant activity could be effected. The hemorrhagic zones were mapped out in the standard sections for comparison with a group of fourteen control animals (Table II). It is apparent that the infarcts in the group which received anticoagulants were significantly more hemorrhagic; however, one infarct in the control group was almost entirely hemorrhagic, and two dogs which received anticoagulants had no evidence of hemorrhage in their infarcts.

All control animals which lived for three days after an infarct was produced survived indefinitely. On the other hand, of the group which received anticoagulants and survived at least three days, eight of twenty (40 per cent) died before the termination of the study on the twelfth day. One must conclude, then, that anticoagulants in this study increased the hemorrhagic character of the infarcts and also increased the hazard to the animals. It should be emphasized that this applies to fresh hemispheric infarcts that are completed.

In another group of dogs, the infarcts were produced by forty-eight-hour homologous blood clots.[20] These animals had received anticoagulants (tromexan and dicumarol) for two days prior to the day on which the infarcts were produced, so that therapeutic reduction of prothrombin activity existed at that time. The prothrombin activity was maintained close to the therapeutic range. The problem of hemostasis was increased at the time of the operative procedure for the injection, but it was by no means insurmountable.

Since this method of production of infarcts constitutes a shower of clot fragments, or emboli, we tried to estimate whether there was any protection afforded the dogs which were given anticoagulants prior to injection of the clots. This was done by comparing the total area of infarction in the seven standard sections with the findings in a control

TABLE IV. EFFECT OF ANTICOAGULANTS ON EXTENT OF HEMORRHAGE IN CEREBRAL INFARCTS PRODUCED BY CLOTS

Hemorrhage, Per Cent	Control Dogs		Dogs Given Anticoagulants	
	Number	Per Cent	Number	Per Cent
0-30	2	11	2	10
31-60	4	22	2	10
61-90	4	22	4	20
91-100	8	44	12	60

group. This comparison was limited to those infarcts more than twenty-four hours old, so that they would be well demarcated (Table III). A slight difference was noted in favor of the dogs which received anticoagulants, but it was not striking. Likewise, the over-all percentage of animals which had infarcts in this group was not significantly different from that usually obtained by injection of clots. Despite a therapeutically reduced prothrombin activity at the time of the injection of the clot, fragments of clot were found grossly in the major arteries at or near the base of the brain in almost half of the animals.

As noted previously, infarcts produced by injection of homologous clots are relatively hemorrhagic lesions even in the absence of influence from other agents. We have compared a group of controls of this type with a group which received anticoagulants (Table IV). A wide range in the extent of hemorrhage occurred in each group, and the anticoagulants apparently had little effect on the cerebral infarcts when compared with control infarcts that ordinarily have a hemorrhagic character. The relatively small differences indicated in the incidence of infarcts with maximal hemorrhage are not statistically significant. However, the slight difference noted in Table IV is increased by the knowledge that frank hemorrhage was present within two of the infarcts in the dogs receiving anticoagulants, in one of which intraventricular hemorrhage was noted. This was not seen in any of the infarcts of the control animals. Including all our studies, hemorrhage has not been seen in the brain of an animal which received anticoagulants, unless it was within an infarct or had ruptured into the ventricles.

Comment

It should be emphasized that these studies are not an attempted indictment of the clinical use of anticoagulants in cerebrovascular disease. It is noteworthy that, whenever an excessively hemorrhagic infarct was present, it occurred in recently produced, completed infarcts in one hemisphere. There is little evidence, clinical or experimental, that anticoagulants are beneficial in this particular category of cerebrovascular disease. It is hoped that the results of studies such as these will be used as a "caution sign," so that the indications for and limitations of anticoagulant therapy will be clearly distinguished.

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AMERICAN HEART ASSOCIATION SPONSORS NBC-TV SERIES TO INTEREST YOUNG PEOPLE IN RESEARCH CAREERS

A series of television programs designed to interest high school and college students in careers as research investigators in the biological sciences will be sponsored by the American Heart Association and presented as an educational program of the National Broadcasting Company for thirteen consecutive weeks beginning March 24.

Supported in part by E. R. Squibb and Sons, the live half-hour programs will be shown over most stations of the National Educational Television network on Mondays at 6 p.m. EST. In addition, some NBC stations will carry the live programs.

The series, first of its kind designed to help fill the need for capable young people in medical research, will bring to the viewer the flavor of investigative work and the stimulating world which it represents. Various areas of research in the medical and biological field will be discussed each week by leading cardiovascular investigators. The background of an important research problem will be dramatically documented from its early history to its present status.

The entire series will be kinescoped for later showings on regular network stations and on additional stations of the Educational Television network. Local Heart Associations will show the kinescopes at classes and science clubs and in connection with their Health Careers programs.

Diseases of Small Arteries and Arterioles

Emphasizing Fibrinoid and Hyaline Changes

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THE FIBRINOID CHANGE represents a morphologic alteration involving small arteries and arterioles which occurs in several major vascular diseases. These diseases include such varied entities as malignant or accelerated hypertension, eclamptic toxemia of pregnancy, diabetes mellitus, the collagen diseases especially when associated with an arteritic component, thrombotic thrombocytopenia and symmetrical renal cortical necrosis. Moreover, certain experimentally induced states also express themselves morphologically by the presence of "fibrinoid" within small arteries and arterioles. Notable among these are the experimentally induced hypertensive cardiovascular states and the disturbances associated with the generalized Shwartzman reaction.

It follows that "fibrinoid," as encountered in small arteries and arterioles, represents a fundamental reaction which must be reckoned with in any consideration of the pathogenesis of the various disorders in which it is encountered.

Observers interested in the above listed group of diseases have concerned themselves with the characteristics of fibrinoid and have, from time to time, considered the complex problem of the genesis, the meaning and the disposition of this material.

Altshuler and Angevine[1] made extensive studies dealing with the problem of fibrinoid and added to the appreciation of this material. According to these workers, a common feature of fibrinoid formation is the precipitation of acid mucopolysaccharide from the ground substance of connective tissue. This disturbance was considered to give rise to the formation of a homogeneous, eosinophilic, relatively acellular substance with some properties of fibrin as described by Neumann. In these studies, distinction between fibrinoid as encountered in connective tissues and that within blood vessels was not stressed.

More recently, interest in fibrinoid has received major impetus by observations dealing with this material as observed in association with the Shwartzman phenomenon and in the collagen diseases by Thomas, Good, Smith, Brunson and co-workers.[2-8] These workers have stressed the possibility of a hematogenous source of fibrinoid in these conditions.

Brunson and co-workers clearly described the disposition of fibrinoid in the Shwartzman reaction and depicted certain of its histologic properties. The possibility that this material may be derived from fibrinogen or altered fibrinogen was entertained. Potentiation of the "fibrinoid deposits" by acidic polymers was demonstrated while heparin appeared to play a protective role. In essence, the hypothesis considered by these workers placed the fibrinoid of the Shwartzman reaction in the role of an infiltrative or embolic material derived from altered plasma proteins.

The diseases which are attended by the vascular and connective tissue fibrinoid changes may be associated with the development of proteins in the plasma which are precipitated in the cold by heparin.[8] These proteins have certain characteristics of fibrinogen.

The use of the fluorescent antibody technique of Coons has indicated the presence of fibrin within the fibrinoid of connective tissues as well as within the fibrinoid of blood vessels.[9] Whether the fibrin present results from the permeation by plasma proteins (including fibrinogen and its product fibrin) of a non-hematogenous substance ("fibrinoid"?) previously developed within the blood vessels or whether it represents a primary disturbance remains to be demonstrated.

This brief consideration may be taken to indicate a widespread occurrence of the material known as fibrinoid in a series of vascular diseases

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TABLE I. MAJOR STAINING AND HISTOCHEMICAL FEATURES OF FIBRINOID

Material	H and E	Mallory Aniline Blue Masson Trichrome	PAS	Lipids Oil Red O Sudan Black B Nile Blue Sulfate Schultz	Free Carbonyl	Protein SH	K	Congo Red	Xantho-proteic	Millon	Indole	CA
Vascular Fibrinoid	Eos.	Red	Purple. (+)	+	+	+	+	+	—	—	—	—
Connective Tissue Fibrinoid	Eos.	Red	Purple (+)	—	—	—	—	—	+	+	+	+
Fibrin	Eos.	Red	Purple (+)	—	—	Weak +	Weak +	Weak +	+	+	+	+

which likely are initiated by different primary causes. Approaching the problem from this view, it is plausible to expect a common means for the development of this morphologic expression of injury in these various states. The two concepts mentioned above have attempted to explain this common path of expression by invoking, on the one hand, changes in the ground substance of connective tissue and, on the other, the deposition of materials having a hematogenous source.

Our interest in the problem of the fibrinoid changes in small arteries and arterioles began with observations of the hypertensive cardiovascular state following renal ablation of the dog.[11] Subsequently, observations were extended to include tissue changes in malignant and benign hypertension of man, in kidneys from patients having suffered from diabetes, renal cortical necrosis, thrombotic thrombocytopenia and in the kidneys from rabbits following the Shwartzman reaction. These studies have led us to consider an approach to the genesis of vascular fibrinoid which differs fundamentally from the two approaches mentioned above. The thesis which we support considers that the vascular fibrinoid of these various states is derived mainly from disintegrated vascular smooth muscle. The latter may be termed the concept of the *autochthonous origin of vascular fibrinoid.* Features supporting this concept are considered in this discussion.

Fibrinoid: Connective Tissue versus Vascular Types

Fibrinoid has been described within blood vessels in the conditions listed above and within connective tissues in certain disorders, that is, in rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, as well as in the base of peptic ulcers, between the ends of poor-healing fractures and within the placenta.

In the course of considering fibrinoid it has appeared of advantage to us to distinguish between the "connective tissue" and "vascular" types. This distinction has been made possible, primarily, because of markedly divergent staining and histochemical characteristics.[10]

Major staining and histochemical features of fibrinoid are given in Table I. With the procedures used it is evident that connective tissue fibrinoid, as observed in certain conditions, gives certain staining and histochemical reactions similar to those of fibrin. Both materials were eosinophilic, intensely red with Mallory's aniline blue and Masson's trichrome stains and positive (purple) with the periodic acid-Schiff reagent (PAS) procedure. Both ingredients failed to yield evidence for the presence of various lipids and free carbonyl groups. Fibrin gave weak reactions for protein-bound SH, free potassium and acid esters of polysaccharide origin (using Congo red) while connective tissue fibrinoid was negative for these procedures. Both fibrin and connective tissue fibrinoid gave distinctly positive reactions with the xanthoproteic, Millon, indole and calcium reactions.

The histologic pattern for vascular fibrinoid has been consistent. The material was eosinophilic, red with Mallory's aniline blue and Masson's trichrome stains and purple (positive) with the PAS procedure. With these approaches, vascular fibrinoid, connective tissue fibrinoid and fibrin were similar. Vascular fibrinoid, however, yielded intensively positive reactions with various lipid-demonstrating procedures and with the procedures for free carbonyl groups, for protein-bound SH and for free potassium. The Congo red procedure was positive when frozen sections were used. On the other hand, xanthoproteic, Millon, indole and calcium reactions were negative.

In summary, with certain procedures vascular and connective tissue fibrinoid are similar in appearance. With other procedures these two ma-

terials give reactions which mirror each other (staining patterns are reversed) as depicted in Table I. The characteristics of vascular fibrinoid emphasize an eosinophilic appearance, a positive reaction for free aldehyde groups of polysaccharide origin (PAS) and acid esters of polysaccharide origin (Congo red), positive reactions for various lipids and fats (oil red O, Sudan black B, Nile blue sulphate, Schultz reaction), positive reactions for free carbonyl groups, protein-bound sulf-hydryl groups and free potassium. The term "vascular fibrinoid" as considered in this discussion, is thus reserved for material encountered in various vascular disorders which stress these characteristics.

Fibrinoid and Vascular Diseases

The appearance and distribution of "vascular fibrinoid," as identified by the characteristics listed above, in various vascular diseases and experimental states may be utilized in support of a concept considering its origin.

1. *Renal Ablation of Dog.*[11-18]—Bilateral nephrectomy of the dog under certain conditions is attended by systemic arterial hypertension and the development of cardiovascular lesions. The vascular lesions involve especially the small arteries and arterioles which constitute the intrinsic vasculature of the viscera. The appearance of the arterial and arteriolar lesions, in turn, is mostly dependent on the management given this experimental preparation.

A high intake of sodium[19] or a lesser intake of sodium plus a protein-containing diet[20] is associated with a rapid rise in the arterial pressure and widespread disruption of small arteries and arterioles. Prolongation of life by electrolyte balance, diet and dialysis alters appreciably the characteristics of the arterial-arteriolar lesions. In both the acute and the subacute-chronic phases of this preparation "vascular fibrinoid" is encountered. By arresting the course of this experimental preparation at various times, a sequential relationship can be demonstrated for the various expressions of the vascular disease.

Fulminant Acute Phase.—A rapid disruption of arteries and arterioles in the renoprival state is attended by the development of "fibrinoid" within the walls of these vessels. The relationship of this material to the vessel wall and its distribution are considered pertinent to the concept of its origin.

The fibrinoid is found overwhelmingly within the area of the media where smooth muscle normally exists. The appearance of the fibrinoid describes an inverse relation to the presence of smooth muscle. Where only a segment of the circumference is involved, this segment is in direct continuity with the normal appearing media. More important, however, are transitional changes between the normal muscle and the fibrinoid. In the transitional zone, swollen muscle fibers with pyknotic nuclei may be seen. Non-nucleated masses with the configuration of swollen muscle fibers may be seen and the substance of these masses has the characteristics of "vascular fibrinoid." These individually swollen masses, which are considered to represent damaged smooth muscle fibers, mesh imperceptibly with the typical fibrinoid material. It is possible to encounter the area of the inner half of the media showing the fibrinoid change while the outer half has intact smooth muscle. Centripetal spread of the fibrinoid into the lumen by contraction of the rim of smooth muscle near the adventitia appears plausible.

The fibrinoid in the media appears to have properties of a hydrogel. At any rate, it may spread into the adventitia in a pseudopod fashion or it may be continuous with similar material within the lumen. In the lumen the configuration may be that of a polypoid mass or it may fill the lumen. In areas where the fibrinoid appears smeared and spread out, intact erythrocytes may be seen within its substance. The endothelium may or may not be disrupted but classical thrombosis is not observed. Capillaries which are obstructed and distended with fibrinoid may be encountered in the vicinity of arteries and arterioles displaying the fibrinoid change.

Subacute and Chronic Phase.—Dogs which are sustained by dialysis for ten to over 100 days following renal ablation not only maintain the hypertensive state but the characteristics of the arterial and arteriolar lesions are altered. Within ten to thirty days the fibrinoid changes, as described above, become less prominent. The material in the media begins to assume the appearance of hyalin. Occasionally nuclear remnants are seen within the hyalinizing substance. Later there is distinct hyaline thickening of arterioles. Along with the hyaline changes, connective elements are

observed in the intima, media or adventitia. Such vessels display narrowed lumina and thickened walls. The characteristics are those of arteriolarsclerosis.

The hyalin of the hyaline arteriolarsclerosis following renal ablation displays the staining and histochemical characteristics of "vascular fibrinoid" although by ordinary stains it appears compact and smoother than fibrinoid. Just as transitional changes are observed between the smooth muscle of the media and vascular fibrinoid, so transitions may be encountered between vascular fibrinoid and vascular hyalin.

2. *Essential Hypertension in Man.*[11,15-17]—In the accelerated form or malignant hypertension of man "vascular fibrinoid" is encountered. Although the material may be observed in the arterioles of various viscera, such as pancreas and periadrenal area, it is most prominent within the kidney. The characteristics and configuration of this material are identical to those encountered in the dog following renal ablation.

Of particular interest is the encounter of elongated or globular masses of "fibrinoid" of the vascular type within the glomeruli in malignant hypertension. In isolated examples it is possible to encounter fibrinoid in the wall of the afferent arterioles, within their lumina and from here in direct continuity with the same material in glomerular capillaries. This association led to the suggestion that the glomerular fibrinoid was derived from the arteriolar fibrinoid by embolization. For the same reasons given in the section on renal ablation the origin of the arteriolar fibrinoid of malignant hypertension from vascular smooth muscle has been proposed. This is in keeping with the view of workers who have designated this lesion as arteriolarnecrosis.[21]

In benign hypertension, the arteriolar hyalin appears identical to that described above following renal ablation plus prolonged survival. In a study destined to compare the characteristics of the hyalin of benign arteriolarsclerosis with the acute arteriolar lesions of malignant hypertension, both gave the characteristics of "vascular fibrinoid" and the only difference detected between them was the absence of acid phosphatase in the hyalin lesion while it was detected in the necrotic ("fibrinoid") lesion. Both revealed similar microspectroscopic features as obtained by ultraviolet absorption.

3. *Thrombotic Thrombocytopenia.*—Since the early description of this entity, a vascular component in its pathogenesis has been appreciated. Whether the vascular component results mainly from thrombosis or embolism or whether it results from a primary intrinsic vascular lesion has been the source of various considerations. Orbison and co-workers[22,23] and Gore[24] championed a primary vascular lesion. Orbison alluded to the fibrinoid change in the blood vessels. Fisher and Creed[25] more specifically designated the vascular changes as of fibrinoid type.

One of the main vascular disturbances in thrombotic thrombocytopenia results from the development of occlusive masses in small arteries and arterioles. These vessels in turn become distended in an aneurysmal fashion. A compromise of the circulation within the viscera transpires and areas of ischemia and infarction develop. Neurologic manifestations become outstanding. At the same time a hemolytic anemia is present and a fluctuating thrombocytopenia of varying proportions occurs.

Orbison described a similarity between the appearance of the occlusive masses and certain changes within the arteriolar wall.[22,23] Orbison also recognized similarities between the lesions of thrombotic thrombocytopenia and certain vascular lesions of the nephrectomized dog,[19] especially following the explosive vascular disruption attendant on renal ablation plus a high sodium intake.

We have confirmed Orbison's findings in demonstrating lesions in the nephrectomized dog which closely resemble those of thrombotic thrombocytopenia.[18] Moreover, in the latter lesions both the occlusive masses and the arteriolar wall describe the characteristics of "vascular fibrinoid." These two components (luminal and mural) are frequently continuous with each other. Based on other experiences with the nephrectomized preparation alluded to above, we have interpreted these lesions in the dog as derived mainly from vascular smooth muscle.

It is of interest that the occlusive masses as well as the vascular wall in a case of thrombotic thrombocytopenia studied in our laboratory yielded the characteristics of vascular fibrinoid. This suggests that the material in the wall of the arteries and arterioles which appears to give rise to the primary base of the occlusive masses has a derivation similar to that following renal ablation of the dog and in malignant hypertension of man.

4. *Bilateral (symmetrical) Renal Cortical Necrosis.*—This remarkable entity occurs mostly (60 per cent of cases) in pregnancy.[26] Of prominence is ischemic necrosis of the renal cortex which, in turn, is considered to result from a vascular disturbance. The lesion is reproduced experimentally in the Shwartzman phenomenon or by the injection of bacterial toxin directly into the renal artery without a preparatory dose.[27] The details of the pathogenesis remain obscure. Intense congestion of the glomerular and peritubular capillaries occurs.[28] In addition, the fibrinoid change involves the wall of interlobular arteries and occlusive masses of fibrinoid may be seen in the lumen of these vessels and in the glomeruli.[27,29] The fibrinoid in this entity has the characteristics of "vascular fibrinoid."

5. *The Kidney in the Shwartzman Reaction.*[30] —The renal cortical necrosis due to the Shwartzman reaction is associated with the deposition of fibrinoid within the interlobular arteries, arterioles, glomeruli, tubules and peritublar areas of the kidney. In all of these locations the fibrinoid displays the characteristics of vascular fibrinoid. Transitional changes between the intact vascular smooth muscle and the fibrinoid in the media may be observed just as in the experiments on bilateral nephrectomy of the dog. Fibrinoid within the area of the media of interlobular arteries may be limited by a thin membrane on the luminal and in the adventitial sides. On the luminal side this appears to be the basement membrane of the endothelium. The presence of this membranous remnant may be taken to favor a medial origin as opposed to an infiltrative origin. The fibrinoid may replace precisely the area of the media within twelve hours or less following the second dose of bacterial toxin. Continuity between the fibrinoid in the media and polypoid masses in the lumen of the vessel may be observed. The latter are similar to those seen following renal ablation of the dog, in thrombotic thrombocytopenia and in renal cortical necrosis.

The similarity between the vascular fibrinoid of the Shwartzman reaction to that following renal ablation, the seeming transitional changes between normal vascular smooth muscle and this fibrinoid and the confinement to the media in some aretries led us to suggest a major contribution from disrupted vascular smooth muscle to the make-up of this substance.

6. *The Kidney from Diabetic Subjects.*[31]—The lesions of diabetic glomerulosclerosis frequently include two major components: a nodule with peripheral cells and a core having the staining characteristics of collagen, and globular, elongated or crescentic eosinophilic and acellular masses which have the characteristics of vascular fibrinoid. The cellular nodule may be surrounded by dilated capillaries or by crescented masses of fibrinoid. Fibrinoid with the same characteristics as that within the glomeruli is also observed in the wall and lumen of the afferent arterioles, within the capsular space and within the tubules. The impression has been gained that the glomerular, capsular and tubular fibrinoid are derived from the arteriolar fibrinoid by embolization and escape into the tubules.

Fibrinoid Derived from Autolyzed Normal Smooth Muscle[32]

In the above treatment, "vascular fibrinoid" has been described in a group of disorders which not only seem to be initiated by different etiologies but which also express themselves differently from a clinical standpoint. In each entity, the walls of small arteries and arterioles, the lumina of these vessels and that of nearby capillaries may contain the substance designated as "fibrinoid." The concept that this "vascular fibrinoid" is derived largely from vascular smooth muscle has been proposed mainly as a consequence of a series of inferential considerations. The findings upon which this view is based include the location of the fibrinoid material precisely within the media, the disappearance of normal smooth muscle as the material appears, the rapid appearance of the material (a few hours) in some states, the direct continuity of the material with normal appearing media, transitional changes between the normal muscle and the material and certain similarities in the staining, histochemical and microspectroscopic characteristics of the material and normal vascular smooth muscle. In view of the possible relationship between vascular smooth muscle and fibrinoid it was decided to determine whether normal smooth muscle subjected to autolysis and disruption in the test tube develops characteristics of vascular fibrinoid.

For this purpose smooth muscle from the stomach and colon of the dog was obtained under sterile conditions. After autolysis, it was macerated in a Waring blender and gross particles were

removed. The fine particles were centrifuged into a button. Grossly in the test tube, and after smearing on a slide, this material had the appearance, staining and histochemical characteristics of vascular fibrinoid.

By passing the autolyzed smooth muscle through meshes of decreasing porosity it was possible to develop a suspension which passed readily through needles of 23 to 25 gauge. The material was injected into the renal artery of the dog and the kidneys were observed after from three to twenty-four hours (acute phase) and after one to eight weeks (subacute phase).

Acute experiments.[32]—The particles of autolyzed smooth muscle lodged within interlobular arteries, arterioles and glomerular capillaries. Moreover, the material was observed free in the capsular spaces, as casts in the tubules and in the peritubular areas apparently within peritubular capillaries. In all sites the injected material displayed the characteristics of vascular fibrinoid. In most sites of deposition the material failed to evoke an inflammatory response. Occasionally an occluded interlobular artery developed necrosis of its wall superimposed by scattered inflammatory cells (arteritis). Focal or total necrosis (infarction) of the glomerulus also occurred.

Where the occlusive masses were associated with injury of the arterial wall, the media of the injured vessel assumed the characteristics of vascular fibrinoid. Here there were two sources of fibrinoid, that derived from the injected autolyzed smooth muscle and that derived *in situ* from the smooth muscle of the media of the artery.

These acute experiments demonstrated the derivation of "fibrinoid" from smooth muscle and the ability of the material to flow and lodge within the vascular and tubular conduits of the kidney. Indeed, in an occasional experiment the "fibrinoid" could be injected into one renal artery and later observed within the vasculature of the opposite kidney.

Subacute experiments.[33]—Study of the kidneys injected with autolyzed smooth muscle one to eight weeks after the injection added to an understanding of the behavior of this material *in vivo*. In these experiments, one kidney was removed and this kidney acted as the control for future comparison. The remaining kidney was injected and replaced in its bed for one to eight weeks. At various times the kidney was obtained and studied microscopically.

The fibrinoid material had the same appearance after one to eight weeks as it did when observed shortly after the injection. The material was present in small arteries and within glomerular capillaries and in each site it had the characteristics of vascular fibrinoid. Because the characteristics were preserved, we believe the vascular material seen at one to eight weeks was the same as that injected.

Within the small arteries the fibrinoid formed polypoid masses which protruded into the lumen. These were covered by endothelium and usually evoked no inflammation or secondary thrombosis. Within the glomeruli, the fibrinoid had the same appearance but here there was usually cellular proliferation about it.

Remarkable features in the subacute experiments consisted of the development of glomerular lesions. These lesions resembled in some respects those observed in the glomerulus in diseases of man associated with vascular fibrinoid. The major morphologic alterations were:

(a) *Membranous thickening of the glomerular capillary wall resembling "diffuse intercapillary sclerosis" and the "wire loop" lesion.*—The capillary wall or the "intercapillary area" became thickened by the accumulation of a hyaline material. The capillary was patent and retained its endothelial lining but it frequently was narrowed by the thickened wall. On cross-section the capillary displayed the so-called "wire loop" configuration. An occasional lobule appeared to have been destroyed by this lesion.

(b) *Increased cellularity.*—Increased glomerular cellularity assumed several expressions. Small elongated cells accumulated concentrically about the remaining "fibrinoid" globs. Capillaries showing hyaline thickening in their walls at times displayed cells in the wall or what appeared to be increased numbers of endothelial cells. Clumps of cells resembling endothelial cells were seen. In some areas a diffuse cellularity of types seen in certain forms of glomerulitis was evident.

(c) *Nodular lesions.*—Nodular lesions were observed in the center or in the periphery of glomerular lobules. These numbered one to three. The center (or core) appeared to be hyalin and the

periphery contained cells. These nodular changes displayed features reminiscent of the lesions seen in diabetic glomerulosclerosis and in certain forms of membranous glomerulitis.

(d) *Thickening of Bowman's capsule.*—The parietal layer of Bowman's capsule displayed hyaline thickening. The epithelium covering of the capsule seemed intact.

The hyaline substance causing thickening of the glomerular capillaries, the hyalin of the nodular lesions, the hyalin which was associated with destruction of the glomerular lobules and the hyalin in the thickened Bowman's capsule failed to reveal the pattern of staining and histochemical reactions characteristic of vascular fibrinoid. This material was eosinophilic and positive (purple) with the PAS procedure. It failed to yield a positive reaction for lipids and for other substances observed in vascular fibrinoid. With Mallory's aniline blue stain this hyaline material was blue, with Masson's trichrome stain it was green and with Mallory's phosphotungstic acid hematoxylin it was orange-brown. From these observations it appeared that the injected autolyzed smooth muscle initiated a reaction within the glomerulus characterized by the deposition of a hyalin different from the usual arteriolar hyalin. There is the possibility that this seemingly secondary hyalin was deposited under the influence of cells within the glomerulus, either the normally present endothelial and epithelial cells or the cells which undergo proliferation.

General Comment

This consideration of the substance designated "fibrinoid," as it is encountered in a group of vascular disorders, has served to emphasize one view as available in published works. In so presenting the subject, it is realized that the matter in its present state is a controversial one. It is encouraging, however, to be aware of different approaches which attempt to develop a better understanding of the origin and significance of fibrinoid as observed in blood vessels.

The ultimate cause and source of the fibrinoid of blood vessels is of more than passing morphologic interest. An understanding of this material may well be necessary for the final understanding of major vascular disorders which remain obscure. In the process of searching for means of developing this understanding it seems important whether the material is an infiltrate of hematogenous origin or a product of autochthonous development.

Should vascular fibrinoid have its main origin from vascular smooth muscle, then emphasis should be toward a better understanding of the fundamental causes of smooth muscle injury.

Assuming that vascular fibrinoid is derived mainly from vascular smooth muscle then it would seem that different etiologies of vascular disease may affect the same morphologic end product. That different basic etiologies pertain in the varied vascular disorders herein considered appears quite likely. Certain of these states are associated with systemic hypertension; others are not; some are localized (renal cortical necrosis) while others are generalized (thrombotic thrombocytopenia); inflammation of the arterial and peri-arterial zones may be prominent in some (the arteritides) while minor or absent in others (malignant hypertension); extravascular disturbances may be outstanding in some (hemolytic anemia and thrombocytopenia in thrombotic thrombocytopenia) but not so prominent or absent in others (Shwartzman reaction). These variations are reflected by varied clinical expressions.

The disorders which emphasize fibrinoid in the arterial wall are also associated with the presence of fibrinoid in an extramural location. Major sites of deposition are: the arterial lumen adjacent to the mural involvement; the lumen of capillaries near sites of arterial involvement; the glomerulus; the capsular space of the glomerulus, and renal tubules. Within renal tubules the material appears to become incorporated in casts. This suggests its ultimate presence in the urine.

In order to explain the presence of fibrinoid in sites away from the arterial wall, the concept of an autochthonous arterial origin of this material must invoke migration of the fibrinoid away from its site of origin. The material appears to possess the property of swelling and spreading. Thus continuity between the material in the arterial wall and that in the lumen, on the one hand, and that in the adventitia, on the other, is often encountered. Migration into the lumen is conceivably aided by muscle fibers remaining near the adventitia as well as by the external elastic lamina, when present. A material prepared artificially from normal smooth muscle flows in the blood stream and lodges at different sites. Of particular interest is the demonstration of rupture

through the glomerular capillaries and subsequent lodging in renal tubules.

Certain disorders which emphasize vascular fibrinoid are associated with serious glomerular disease. The glomerular disturbances reflect themselves structurally by capillary or intercapillary thickening (membranous glomerulitis, wire loop lesion), increased cellularity and, in special circumstances, by production of nodular lesions. Focal necrosis of the glomerulus also is encountered. These changes move toward ultimate destruction (sclerosis) of the glomerulus and bring secondary tubular changes. The conditions which are attended by these glomerular alterations may also display the deposition of fibrinoid in the glomerulus. It is therefore of interest that an artificial product of normal smooth muscle which resembles vascular fibrinoid is capable of evoking glomerular alterations which, in turn, resemble alterations encountered in the vascular fibrinoid diseases.

Summary

1. Fibrinoid formation is a structural change which occurs within connective tissues and blood vessels in a variety of disorders. Vascular fibrinoid may be distinguished from connective tissue fibrinoid according to its tinctorial properties.

2. Vascular fibrinoid occurs in a variety of conditions including malignant or accelerated hypertension, eclampsia, diabetes mellitus, the collagen diseases, thrombotic thrombocytopenia and renal cortical necrosis. Vascular fibrinoid emphasizes the presence of fats and lipids, free aldehyde groups of polysaccharide origin, acid esters of polysaccharide origin, free carbonyl and protein-bound (SH) groups and free potassium.

3. Reasons for considering the main contribution to formation of vascular fibrinoid by the disintegration of vascular smooth muscle have been presented.

4. Autolyzed normal smooth muscle displays the characteristics of vascular fibrnoid both in the test tube and in the body.

5. Autolyzed smooth muscle, when injected into the kidneys, appears capable of initiating certain glomerular lesions which include increased cellularity, membranous and nodular changes.

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Purpuras and Associated Thrombotic Conditions

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THE BASIC MECHANISMS concerned with hemostasis are four: vascular integrity, the platelets, plasma coagulation factors, and finally, the anticoagulant and fibrinolytic systems.

In most situations involving refractory bleeding or purpura, more than one of these mechanisms are concerned. Thus, platelet deficiencies and impaired vascular integrity commonly go together, and sometimes coagulation and vascular defects are associated.

In this discussion, attention will be directed to vascular abnormalities and platelet deficiencies with only passing references to disorders involving plasma coagulant and anticoagulant or fibrinolytic factors.

The integrity of small arterioles and capillaries may be altered, in a descriptive sense, by increased fragility or by enhanced permeability. Structurally, the capillary consists of a fibrillary membrane, an endothelial cell layer, and cement substance, which binds the cells together. Functionally, the capillary (besides serving as a partially permeable channel) has retractile, contractile, and adhesive properties which, for the most part, are not well understood.

It is known that the cement substance contains hyaluronic acid, and that ascorbic acid, calcium, and probably vitamin D play roles in its formation.

It has been observed that immediately after injury the normal capillary will retract and constrict. This effect lasts only fifteen to thirty seconds and more prolonged constriction is brought about by a substance released from lysed platelets. This material was formerly thought to be serotonin and serotonin undoubtedly does play a role in vascular behavior. But the platelet factor responsible for capillary vasoconstriction is probably not serotonin, and for the present is best termed simply "platelet vasoconstrictor factor."

Furthermore, capillary vessels respond to the plasma content of histamine, which promotes dilatation and increased permeability, and to the concentration of hyaluronidase at the layer of cement substance, which has a dissolving effect.

It seems to be well demonstrated that the adrenal cortex is concerned with capillary permeability possibly through the mediation of a specific steroid, thrombocytosin, released in response to ACTH stimulation.

Usually, where capillary permeability is affected (as in the purpuras) fragility is also involved. Examples are scurvy, drug sensitization and idiopathic thrombocytopenic purpura. But the converse is not necessarily true. Thus, in hereditary hemorrhagic telangiectasia the vessels may be exceedingly fragile but they do not exhibit greater permeability than is the case with normal endarterioles and capillaries.

It has seemed fitting to approach the subject of purpura from the standpoint of a patient with a bleeding disorder. The points deserving particular emphasis in taking the history and performing the physical examination in a patient suspected of having a bleeding disorder are listed on Tables I and II.

The number and complexity of laboratory examinations required for comprehensive analysis of some hemostatic defects are fortunately not required in the great majority of bleeding disorders. Moreover, relatively simple procedures serve to disclose the general nature of the abnormality and, where applicable, indicate the use of more elaborate and definitive tests. It is, nevertheless, of the greatest importance that exact techniques be carried out with care in the performance of the simplest examinations, since they at best are only roughly qualitative and if improperly done may be grossly misleading. On Table III are shown the most important initial or screening tests as well as some of the more specialized examinations and laboratory approaches useful in particular circumstances.

Proceeding from the general examination of a patient we may consider etiologic classification

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From the Thomas Henry Simpson Memorial Institute for Medical Research, Ann Arbor, Michigan.

TABLE I. HISTORY

Characteristics of Bleeding	
How?	Overt; occult; bruisability; other
Where?	Site or source; local; generalized
How Long?	Definite; indefinite; lifetime
Onset?	Abrupt; insidious; unknown
When?	Persistent; recurrent; cyclic
Course?	Mild; progressive; variable; fulminant
Circumstances Associated with Bleeding	
Spontaneous:	May be any hemorrhagic manifestation
Traumatic:	Often hematoma, hematocele, or refractory bleeding as from dental extraction or minor injury
Menstrual:	Hypermenorrhea; premenstrual epistaxis or purpura
Orthostatic and Mechanical:	Localized purpura
Factitious and Psychogenic:	Epistaxis; cutaneous, gastrointestinal and genitourinary bleeding
Etiologic Considerations with Respect to Bleeding	
Congenital or familial incidence	
Drug intoxication or idiosyncracy	
Food or other sensitization	
Occupational or other contacts	
Dietary habits with reference to deficiencies	
Symptoms of associated illnesses—almost any systemic disease may have purpuric manifestations	

TABLE II. PHYSICAL EXAMINATION

Special Features with Reference to Bleeding Disorders
Kind and site or source of bleeding
Appearance of acute or chronic illness
Developmental abnormalities
Nutritional status
Emotional status
Lymph node enlargement
Splenomegaly—hepatomegaly
Bone (sternal) tenderness

with reference to vascular and platelet abnormalities.

In the matter of thrombosis, as it is related to generalized bleeding disorders, we are concerned with three situations:

1. A chronic, periodic thrombosing tendency associated with excessive numbers of platelets which may be qualitatively deficient, as in the myeloproliferative disorders—chronic granulocytic leukemia, polycythemia vera, essential thrombocythemia and agnogenic myeloid metaplasia.

2. Acute thrombohemolytic thrombocytopenic purpura, a syndrome characterized by acute onset of bleeding, associated with thrombocytopenia, hemolytic anemia, and neurologic manifestations which tend to be migratory and transient, suggesting focal cortical involvement. Hyaline thrombi are present in small arteries of the brain and throughout the body.

TABLE III. LABORATORY PROCEDURES

Screening Examinations
Platelet enumeration or estimation
Capillary resistance test—Rumpel-Leede
Bleeding time—Ivy, Duke
Clotting time—Lee and White
Clot retraction
Lysis of clot
"Prothrombin" time (one stage)
Definitive Examinations
Prothrombin utilization
Thromboplastin generation
Plasma fibrinogen
Ascorbic acid of serum or buffy coat
Special platelet studies
Anticoagulant studies
Special globulin studies
Correction of defect *in vitro*

TABLE IV. VASCULAR ABNORMALITIES

Hereditary and Familial Defects
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)
Vascular Pseudohemophilia (von Willebrand's purpura)
Pulmonary hemosiderosis (idiopathic hemoptysis)
Angiokeratoma corporis diffusum universale (Fabry's syndrome)
Ehlers-Danlos syndrome (mesenchymal dysplasia with cutis laxa, et cetera)
Acquired Defects
Nutritional deficiencies (scurvy, megaloblastic anemias, protein malnutrition)
Allergic sensitization (Henoch-Schönlein purpura)
Drug sensitization
Vasculitis (lupus erythematosus disseminata, polyarteritis nodosa, angio-dermatomyositis)
Infections
Metabolic disorders (renal or hepatic insufficiency)
Tissue hypoxia
Mechanical causes
"Purpura simplex"
Purpura fulminans

TABLE V. PLATELET ABNORMALITIES

Thrombocytopenia—Megakaryocytic
Primary
Idiopathic thrombocytopenic purpura (Werlhof)
Congenital and neonatal thrombocytopenia
Thrombocytopenia with hemolytic anemia (Evans)
Thrombohemolytic thrombocytopenia (Moschcowitz)
Secondary
Acute infections, usually viral
Chronic granulomatous infections
"Collagen" disorders
Congestive and other splenomegalies
Neoplasms, especially leukemias and lymphomas
Drug sensitization reactions (quinidine most important)
Associated with hemangioma in infancy
After excessive bleeding with replacement by multiple transfusions
Thrombocytopenia—Amegakaryocytic
Selective megakaryocytic dysplasia (usually due to drugs, as gold, sulfonamides, et cetera)
Aplastic and hypoplastic anemias
Metastatic and leukemic marrow involvement
Thrombocytopathia
Thrombocytasthenic purpura (Glanzmann's purpura)
Platelet thromboplastin profactor deficiency
Myeloproliferative disorders (granulocytic leukemia, polycythemia vera, agnogenic myeloid metaplasia, essential thrombocythemia)

3. Amniotic infusion with generalized intravascular clotting and resulting defibrinogenation.

The therapy of vascular and thrombocytopenic purpuras may be considered under the following general objectives:

1. Removal of cause when possible, for example, detection and elimination of drug or other allergen, treatment of infection, correction of vitamin deficiency, or eradication of hemangioma by irradiation.

2. Treatment of associated primary disease when not curable, as in case of leukemia, lymphoma, collagen disorders, hepatic or renal disease.

3. Replacement of missing factors supplied by platelets, as by means of fresh whole blood transfusions using siliconized containers, needles and tubing, or by suspensions of separated intact platelets. It is to be expected that preserved platelet fractions or lipids extracted from brain tissue may soon become available for the temporary correction of hemorrhagic disorders caused by platelet deficiencies.

4. Attempts to improve capillary permeability and fragility. This may be done by the administration of vitamin C, and of the bioflavonoids such as rutin, quercetin, hesperidin and esculin; or hormone therapy may be employed, including the use of ACTH, the corticosteroids and the estrogens, such as ethinylestradiol.

5. Attempts to block or diminish the intensity of auto-immune reactions as by the administration of ACTH or corticosteroids, or by splenectomy.

Conclusions

As clinical and laboratory observations on the purpuras have been extended, the complexity of the problem has become more apparent.

With further clarification of the mechanisms of hemostasis which we may expect from the disciplines of biochemistry, physiology, and immunology and from such techniques as protein separation and electron microscopy, it is to be expected that the problems of abnormal bleeding will be simplified and available therapeutic modalities will become more rational and more efficacious.

DISEASES OF SMALL ARTERIES AND ARTERIOLES

(Continued from Page 183)

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Studies on Plasmin: Factors in Lysis of Thrombi

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THROMBOSIS and the lysis of thrombi are of fundamental importance in physiology and pathology as is so well indicated by this conference. Unfortunately, these reactions are complicated, both in the test tube and even more so *in vivo,* and have been made more difficult to understand by the complicated and reduplicative terminology used. In this discussion, we are particularly interested in the last stage of coagulation, the formation of fibrin by the action of thrombin on fibrinogen, and the lysis of this fibrin gel. *In vitro* fibrin can be lysed by many proteolytic enzymes, but *in vivo* the enzyme primarily involved is plasmin or fibrinolysin. But, what is plasmin?

Plasmin is found as an active enzyme in the blood under certain circumstances: with severe trauma, electro-shock, anxiety, after injection of adrenalin, with cyanosis, and in many other conditions. Under usual conditions, however, it is present as an inactive precursor, plasminogen. This precursor has been shown to be a complex of two substances, a proactivator and a proenzyme.

Using streptokinase, the best activator of human plasminogen available to us, the activation pattern is as follows: proactivator is activated by streptokinase and, *in vivo,* to produce activator, which then acts on the proenzyme (plasminogen) to produce enzyme.[1,2] Unfortunately, the kinetics are not sufficiently clear to establish that streptokinase does not act directly on plasminogen to produce plasmin.

Human blood activator will activate not only human, but also, bovine plasminogen and to a lesser extent, the plasminogen of other species.[3] This is the reason for many of our difficulties in studying fibrinolysis. Although plasmin is proteolytic and will digest casein, fibrinogen, and certain other proteins,[4] we are particularly interested in its specific effect on fibrin. It is practically impossible to obtain fibrinogen and thrombin of bovine or human origin, free of plasminogen.[5] Our tests are, therefore, made on artificial proteins, on contaminated substrates or on complicated substrates such as the patient's own plasma or blood (whole clot lysis). All of these give different results, so our evaluations are qualitative.

Present also in the blood are inhibitors for proteolytic enzymes such as trypsin and chymotrypsin, and for plasmin itself.[6] There are at least two antitrypsins and two antiplasmins.[7] These inhibitors combine with active enzyme in a ratio of 1:1 to produce a fairly stable complex. The supposed activation of plasmin by chloroform and other organic solvents is probably on the basis of destruction of this inhibitor, thus permitting spontaneous activation of the enzyme.[8] Significant increase of the inhibitor occurs after major trauma, operations, in some chronic disease,[9] and the infusion of plasmin[10] and may be of importance in the thrombotic syndrome present after surgery and with some chronic disease.

In the discussion of *in vitro* tests and fundamental concepts, it is also important to mention the significance of fibrinogen concentration on fibrinolysis. Dr. Freiman, in our own laboratory, has recently shown that there is a direct relationship between fibrinogen content of a clot and its rate or ease of lysis.[11] This is of great significance in the dilution techniques of determining fibrinolysis, in the whole clot lysis techniques, and probably in the patient.

I should like to propose at this time the following concept (not entirely original) of hemostasis related to the coagulation of blood. Constantly occurring are thrombosis and fibrin formation, and coincidental lysis. Under normal circumstances this is in balance. Even under nearly normal circumstances injuries to vessels take place,

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but extravasation of blood is prevented by a small platelet or fibrin plug or by a thin layer of fibrin on the endothelium. Indeed, Copley[12] has suggested and Loos[13] has shown by ultra microscopy that fibrin is present on the endothelium under normal circumstances. If the platelet plugs are inadequate or the clotting mechanism is badly disturbed, oozing does occur.

With severe trauma and multiple injuries to vessels, fibrinolysin or plasmin is activated, and when this is excessive, not only are fibrin clots and platelet plugs lysed, but fibrinogen is destroyed, along with the other clotting factors (Factors V and VII) and prothrombin, to a lesser degree.[14] This permits the excessive oozing seen at times in surgical and certain complicated obstetrical cases.[15] It is necessary to stress that excessive fibrinolysis may be very short-lived, yet produce serious consequences.[16]

On the other hand, we find increases of inhibitor, and increase of fibrinogen after surgery and trauma, and in disease states.[9] This results not in a hypercoagulable state which everyone has been seeking but a hypolytic state. In other words, the clot now formed has a higher fibrinogen content and is more resistant to lysis. At the same time the normal lytic activity is prevented by a high inhibitor level. It is not hard to imagine this persistent clot at a point of vascular injury, obtaining continuous accretions and becoming a propagating thrombus.

I cannot resist the temptation to suggest that this mechanism may even be a factor in atherosclerosis. Several pathologists,[17,18] Duquid and others, have suggested that thrombi are incorporated in the wall as atherosclerotic plaques. If this be so, then chronic distortion of this mechanism in the direction of hard clots or elevation of the inhibitor could result in persistent thrombus or fibrin formation along the intima with ultimate inclusion. Greig[19] has shown a decrease in fibrinolysis with high fat feedings and we have confirmed this observation.

It is undoubtedly in the field of treatment of intravascular thromboses that plasmin has its greatest promise at present. Plasminogen can be produced in quantity and is non-toxic. However, the best activator at present available (streptokinase) has been very difficult to produce in a sufficiently non-toxic form. It seems likely that this problem will be solved in the near future, since relatively non-toxic streptokinase has been produced and, it is expected, can be produced in sufficient quantity for clinical use in the near future. Methods of purification after activation of the streptokinase are also being investigated and we hope will bear fruit.

Using the impure materials available to us, we started working on this problem in 1952. We investigated plasmin for its effects on normal animals and found that we could produce a significant lytic activity in the blood stream of dogs and rabbits, without significant pathological changes.[20] Subsequent physiological studies have shown that with quantities sufficient to lyse thrombi, oozing from open wounds occurred, but this was easily controlled by cessation of the plasmin infusion or by closing the wound.[21] With much larger doses we could destroy the animal's fibrinogen and perhaps the AcG and other clotting factors partially, but these returned to normal rapidly. In an animal with very high antiplasmin levels (pig), we were unable to develop fibrinolytic activity.

Throughout our experiments we have had difficulties in finding a satisfactory method of producing thrombi. Originally, we used thrombin, but found the clots formed were not sufficiently stable, many disappeared spontaneously within twenty-four hours, and we lost many control rabbits from pulmonary emboli due to leakage of the thrombin.[21] Also the thrombin contains bovine plasminogen and so, it is conceivable, would be lysed more rapidly than a normal clot.[22] We then used sodium morrhuate and most of our studies are on these thrombi. In rabbits, dogs and cats we found that venous thrombi could be lysed, with adequate amounts of plasmin in the general circulation, (4 mgm. plasmin./kgm./weight.)[22] With arterial thrombi, more plasmin (6 or more mgm./kgm.)[23] was necessary. The reason for this is probably a mechanical one, since tributaries into the vein are common, permitting an attack at many points, whereas with the artery, diffusion through a column of stagnant blood must occur, necessitating a higher concentration in the general blood stream. Another theoretical factor is the role of the endothelium in lysis.[24]

Direct observations of the thrombus during the infusion of plasmin answer many of the questions that arise in one's mind about the method of lysis. The distended vein in the area of the thrombus, first begins to decrease in size and lose its blue color; then one notices a little oozing from the needle-puncture hole used for the instillation of

the coagulant. Following this, flow can be seen into the proximal vein, the tips of the thrombus soften and disappear and then the entire thrombus seems to melt away. The entire time from the beginning of the ooze to complete disappearance, is seldom more than ten minutes.

It seems obvious that small segments of thrombus are freed into the circulation, but these have never been of sufficient size to cause any obvious pulmonary embolization, or even observable thrombus in the pulmonary vessels. It is conceivable that the emboli are dissolved in transit or at the time of lodging by the high concentration of plasmin in the blood. Studies with I 131 labeled fibrinogen show increased concentration in the lungs.

In our early experiments, intravenous thrombin was shown to produce death by pulmonary thrombosis in rabbits.[21] A thromboplastic tumor, the Vx2 tumor of rabbits is also known to produce death by multiple pulmonary thrombosis. These two materials were now used to test the efficacy of plasmin for control of pulmonary thrombosis or embolism.[25] Because of the rapid death of the animals it is necessary to give the plasmin immediately after the thrombin or tumor homogenate. In each instance the thromboses were prevented with adequate amounts of plasmin. It may also be of significance that the number of tumor metastases are decreased in the treated animals.

Having satisfied ourselves that plasmin would lyse thrombi in animals, we began to study the effect of plasmin in patients. Despite the lack of reactions in animals, we were reluctant to proceed directly to systemic use in humans. We, therefore, tried the material for local wounds first in 1952 and had success in the treatment of many serious infected wounds and ulcers.[26] More important, is the fact that in over 200 cases, we have had no significant reactions. These include many fresh wounds.[27]

Our first trial of intravenous material in humans was also in 1952. We used plasminogen prepared in our own laboratories and activated with too great an excess of varidase. This, and the next few patients had advanced carcinoma with metastases. Most had some pyrogenic reaction to the varidase used.

Subsequently, the amount of varidase used was decreased to 1000 units, then to 500, and now to 400 units/mgm. of plasminogen.* With these amounts of varidase, reactions have been much less severe and frequent. With the original activated plasmin prepared commercially, reactions were severe, but more recently material has been made available which has minimal pyrogenic effect.**

Studies of the physiological effect of plasmin in humans were carried out as laboratory personnel were available. These were reported previously.[28] There is a significant, but not alarming, fall in fibrinogen, and no significant change in the other clotting factors such as Factor V, Factor VII and prothrombin, with therapeutic concentrations of plasmin. Even with repeated infusions there is significant fibrinolytic activity, and there are indications that this may even increase with repeated injections without increasing adverse reactions or destruction of fibrinogen and other proteins.

The first treatment of a patient for thrombosis was in October, 1953. She had carcinoma *en cuirasse* of the left breast and had had an attempted transnasal hypophysectomy which had to be abandoned because of severe hemorrhage from the carotid artery. Ten days after this operation, the patient developed all the signs and symptoms of a left subclavian and/or axillary obstruction. Eight hours later plasmin was given with marked temporary improvement, including complete relief of pain, pink color returning to skin, warmth and movement of the hand, but there was questionable pulsation. Subsequently, there was regression and amputation became necessary. At postmortem, one month later no thrombus was found.

The first successful case was a seventy-four-year-old white woman receiving radiation therapy for carcinoma of the pancreas, after an exploratory operation. She developed a rapidly progressive thrombophlebitis with severe increasing pain, edema and rubor. Twenty-four hours after the onset with the signs and symptoms still progressive, the patient was given one course of treatment of 3.2 mgm./kilogram. At the end of the infusion the patient had no pain and nor did the pain recur. Her leg decreased in size, although not to normal, during the next seventy-two hours. She was allowed normal ambulation the next day. She survived ten months without evidence of recurrence.

Since the first case, we have treated forty-six patients: twenty-five with venous thrombosis or thrombophlebitis, five of whom had pulmonary emboli; fifteen with arterial thromboses or em-

*Furnished by Ortho Pharmaceutical Co. through the courtesy of Dr. H. O. Singer and Dr. R. V. Chappel.

**Furnished by Merck, Sharp and Dohme.

TABLE I. LEG MEASUREMENTS IN INCHES OF PATIENT R. G.
Before and After Treatment with Plasmin for Bilateral, Old (More than Six Weeks) Thrombophlebitis

	11-28-56		12-3-56	
	Left	Right	Left	Right
Foot	9⅜	9⅝	8⅞	8⅞
Ankle	8⅞	9¾	8½	8¾
Calf	12¼	13¾	11⅜	12½
Knee	14¼	13¾	12¾	12⅝
Lower thigh	18	20⅛	16¼	17⅝
Upper thigh	21¾	22¼	20¼	21¼

TABLE II. LEG MEASUREMENTS IN INCHES OF PATIENT S. L.
Before and After Treatment with Plasmin for Unilateral Thrombophlebitis

	Left		Right	
	12-28-56	1-2-57	12-28-56	1-2-57
Foot	9	9¼	10⅛	9¾
Ankle	10½	10	12¼	11¾
Calf	11½	11¾	14⅜	12⅜
Knee	13⅞	13½	15¾	14¼
Lower thigh	18	18½	22	19⅛
Mid thigh	22	23	25¾	23½
Upper thigh	24½	24⅜ (1-1)	29¼	25½ (1-1)

TABLE III. LEG MEASUREMENTS IN INCHES OF PATIENT R. K.
Before and After Treatment with Plasmin for Pulmonary Embolus

	Before		After Treatment with Plasmin					
	9-11-57		9-12-57		9-13-57		9-16-57	
	L.	R.	L.	R.	L.	R.	L.	R.
Foot	9¾	9⅞	8½	8⅝	8¾	8¾	8¾	8¾
Calf (mid)	12½	13⅛	12	12⅞	12	12	12	12
Thigh	19⅛	19⅝	18¾	18	18	18½	18	18½

Note that the decrease in size followed the relief of symptoms. It should also be noted that this patient was up and about after the third day of treatment so his edema should have increased.

bolism; and two, each, of central retinal artery thrombosis, cerebral thrombosis and priapism secondary to thromboses. The two patients with cerebral thromboses were treated reluctantly, inadequately, and unsuccessfully. No coronary occlusions have been treated, as such, because of our fear of the reactions to the drug in these patients. However, one patient with probable coronary occlusion was treated inadvertently.

At the beginning, we sought to treat the patients as the animals were treated, with one infusion of 4-6 mgm./kilogram. This was generally (though not universally) unsuccessful because of inability to complete the infusion owing to reactions and for other less obvious reasons. These include the fact that these patients were all ill, with high fibrinogen levels indicating clots more resistant to lysis and many had high inhibitor levels. We were never able to reach a level sufficiently high to result in lysis of an arterial thrombus although several showed marked improvement. At the present time, with venous thromboses and pulmonary emboli, our procedure is to give several small infusions, usually two the first twenty-four hours, then one in each of two or three subsequent twenty-four hours. The last treatment may be delayed forty-eight hours. With this regime, we have had excellent success.

Of the twenty patients with venous thromboses receiving adequate treatment, seven had excellent results. An excellent result implies subjective and objective return to normal. Twelve have had good results. A good result implies subjective and some objective improvement. In no case have other treatments been given to these patients before the result has been determined.

A discussion of a few cases will illustrate what we mean by excellent results. Mrs. R. G. and Mrs. S. L. have been reported previously.[29] The former had bilateral thrombosis with marked edema of six to eight weeks' duration, following a pelvic exenteration. She was bedridden because of general weakness, the leg edema, and a staphylococcus septicemia. Furthermore, practically all her peripheral vessels were thrombosed so that parenteral fluids and blood transfusions were almost impossible to administer. After the first plasmin treatment her veins opened sufficiently for easy intravenous infusion and after four treatments her legs returned to normal size and she was able to be up and about in a walker (Table I). She was discharged to fly to her home in Florida two weeks after treatment and had no recurrence of the thrombosis at the time of her death from recurrent cancer more than six months later.

Mrs. S. L., a patient with unilateral thrombosis and edema of an even greater degree, cleared completely after four treatments (Table II).

Our most recent patient, Mr. R. K., a thirty-five-year-old white man was admitted to Ewing Hospital on September 6, 1957, with acute leukemia of two weeks' duration. He had a platelet count of 39,000 which subsequently fell to 32,000. On the second hospital day he complained of pain in a cord over the right ankle. Twenty-four hours later, he had marked calf tenderness, and a markedly positive Homan sign. The next day he had pain in the left chest with a friction rub. His physicians did not wish to use anticoagulants or consider ligation. Twenty-four hours later, five days

after onset, he was given his first infusion of spontaneously activated plasmin, and in six hours a dose of 1.5 mgm./kgm. of plasminogen activated with 400 units of streptokinase as varidase/milligram. After the first treatment, his calf tenderness decreased and after the second, it was almost completely relieved. He had no more chest pain. The chart indicated the improvement as determined by leg measurements (Table III).

This patient makes the fifth patient with a diagnosis of pulmonary embolus or emboli, treated with plasmin. Four had complete regression with plasmin treatment. A fifth patient having all criteria for multiple pulmonary emboli, died of pneumonia and metastatic carcinoma and at postmortem no emboli were seen.

Obviously with arterial thromboses or emboli, this course is impossible and we have used two different methods here. One is to start a plasmin infusion immediately and then remove the embolus at a suitable time. Even with emboli over sixteen hours old, the circulation improves markedly and in one operative case and one postmortem case, the embolus lay free in the vessel, making the removal extremely simple. The other method has been by direct instillation into the thrombus, at operation. Two cases have been reported previously,[29] and we have subsequently had two successful cases at Bellevue Hospital. In only one case have we had success with general infusion.

Discussion and Summary

Therapeutic enzymology is in its infancy, but holds great promise for the future. Plasmin, or fibrinolysin, appears to be the best hope for rapid treatment of thrombotic diseases.

Preliminary studies have shown that it can be given with safety and without serious effect on the animal organism. Pyrogenic reactions at present a serious problem in the human, are undoubtedly due to impurities in the activator. Methods of preparing activator without this disadvantage—either a purified streptokinase, a urokinase, or other activator—are being pressed. It is conceivable that satisfactory methods for purifying plasmin after activation, may be developed even before a better activator is obtained.

Even with the poor and varied materials available, it has been possible to lyse large thrombi, both venous and arterial, of a serious nature in many individuals. However, coronary thrombosis, the most frequent and serious lesion to be encountered, has not been attacked, clinically. There is no reason to suspect that with a nontoxic, nonpyrogenic material this could not be attacked as well. At present, we are investigating the problem of the production of acute thrombi causing infarction in dogs, and the effect on the infarct of this lysis by plasmin, as a preliminary to clinical trials.

The problem of cerebral thromboses or emboli calls for careful investigation. It is conceivable that if the clot were lysed, the sudden return of normal blood pressure to a necrotic area might result in hemorrhage with results worse than the thrombus. We are hopefully awaiting the results of the thorough studies being carried out by Doctor Whisnant, Doctor Millikan, and their group here at the Mayo Clinic.

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The Minnesota Civil Defense Medical Care Plan

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THE MINNESOTA Civil Defense program follows closely the recently revised plans of the Health Office of the Federal Civil Defense Administration. The vulnerability of our target cities to attack with thermonuclear weapons of high potential; the concentrations of population, medical personnel, supplies and equipment, hospitals and industries brings us face to face with the problem of the survival of our nation. For example, an accurately placed 20 megaton bomb, ground burst, without warning, or in the forseeable future—an intercontinental ballistic missile (ICBM)—could destroy both St. Paul and Minneapolis. Approximately one half of Minnesota's physicians, nurses and other health personnel would be eliminated and probably 60 per cent or more of the State's medical supplies, equipment and industrial capacity would be destroyed.

Across the nation similar destruction could occur with the loss of several hundreds of thousands of hospital beds. The sobering realization of the gravity of the national situation made necessary a re-evaluation of the Civil Defense Medical Program. Re-evaluation was necessary to assure the best possible care of non-casualties in order to reorganize industrial production to fight back, in addition to the care of casualties for which most previous planning was directed. The appalling statistics of the National Exercise Alert of July, 1957 (eighteen million dead on the sixteenth day after the attack, thirty-seven million surviving casualties and ninety-five million surviving non-casualties) present a formidable challenge to all health services of the nation. These calculations took into consideration a warning time of two hours, some degree of successful evacuation and/or protection in shelters. The need for intensive medical planning is obvious.

It is becoming increasingly apparent that the care of mass casualties and that of the non-casualty surviving population must primarily be assumed by medical resources in the areas surrounding target cities and that concentration of planning efforts must be undertaken in outlying communities.

The American Medical Association has entered into a contract with the Federal Civil Defense Administration (FCDA) to conduct a study of the medical aspects of Civil Defense. It is to be completed in sixteen months at a cost of $150,000, the funds being provided by FCDA. The study project has been started in the Minneapolis-St. Paul area, and its objectives are:

1. To develop and recommend the planning, training, and operational organization needed as a basis for a National Emergency Medical Care Plan for treatment and care of casualties and non-casualties prior to, during, and after a hypothetical 20 megaton ground burst thermonuclear attack on the United States.
2. To outline the basic role and emergency medical responsibilities of the medical profession in the immediate pre-attack and post-attack period.
3. To outline those functions and responsibilities of the medical profession that may properly be delegated and performed by paramedical personnel under the general direction of the medical profession.
4. To furnish advice and recommendations as to training and education that is needed by all health personnel (professional and non-professional) so that they may be prepared for operational capability in the event of enemy attack.

The AMA Commission consists of six members, two from the Council on National Defense, two from the Council on Medical Services, two appointed by the Minnesota State Medical Association (one representing the Hennepin County Medical Society and one representing the Ramsey County Medical Society) under a staff director, Dr. Earle Standlee. The Commission will seek the advice of the specialty groups of medicine, the allied health professions and other groups that could assist in the conduction of the study project.

Dr. Waldron is also a Doctor of Dental Surgery and a Fellow of the American College of Surgeons. He serves as Deputy Director for Medical Services, Department of Civil Defense, State of Minnesota.

The basic operational facility is the 200-cot (or litter) FCDA emergency hospital (CDEH), or its equivalent in single or multiple units. It is a completely equipped definitive hospital based on a long-range appraisal of post-attack requirements for both casualty and non-casualty medical care. Such facilities would be located 50 miles or more from an anticipated aiming point in the critical target areas of the Twin Cities and Duluth. One of these assembled packaged hospitals is located at Glen Lake Sanatorium, set up as a streamlined display for demonstration and training. A second is located at Moose Lake for training and twelve more are stored in Minnesota institutions. We hope to receive many more; twenty are now on order. It is obvious that FCDA can supply but a relatively small number of the total number of 350 improvised hospitals (70,000 beds) indicated for Minnesota. The staffing pattern for a CDEH includes eleven physicians, six dentists or veterinarians, thirty-three registered nurses and five anesthetists. Trained aides including 100 nurses aides, clerks, messengers, administrative and maintenance staff and helpers increase the personnel to a total of 300 for each CDEH. This staffing pattern is an organization guide for the expansion of Twin City and Duluth hospitals after their site-to-site relocation to cities designated by the Minnesota-Wisconsin FCDA Survival Plan Project. This planning provides for the operation of 35,000 beds and in addition provides a reserve pool of several hundred physicians and dentists for assignment in communities with hospital expansion plans throughout Minnesota. It is obvious that an attack without warning or lack of sufficient time for evacuation would largely cancel out this large potential medical care resource for Civil Defense.

All Minnesota communities with hospitals have made plans to increase the bed capacity of the local hospital as much as possible, and in addition to provide building facilities to make possible a total expansion up to 10 times or more the existing number of hospital beds. For example: City X, population 2,500, a forty-bed hospital and five physicians, is expected to increase its hospital capacity to eighty or more beds and select schools or other suitable buildings for 300 or more additional cots or beds. The staffing pattern for professional workers of the 200-cot CDEH used as a planning guide, calls for eleven physicians, six dentists, two pharmacists, five anesthetists and thirty-three registered nurses. The remaining personnel: 100 auxiliary nurses aides, eighteen trained aides, three first aid technicians, thirty-six clerks, fourteen messengers and sixty-four helpers, make a total of approximately 250 persons. Twice this number would be indicated for City X. The State Office of Civil Defense would endeavor to assign seventeen physicians to assist the five physicians of City X and other professional deficiencies not found by local and county surveys. The Civil Defense director of City X, the hospital administrator and staff, nurses and other groups are responsible for recruiting, training and organizing most of the personnel. By so doing, the Civil Defense Welfare Service of City X would be relieved of the necessity of providing housing and food for up to 500 persons needed for the operation of the 400-bed hospital facilities if brought in from other communities. The State Department of Civil Defense will endeavor to assist all hospital communities in their organization plans. Specific information is being sent to all hospital cities.

The Department of Civil Defense has divided the State into five Mobile Support Areas (MSA), each under an area commander to co-ordinate all CD activities, as follows:

MSA I.—South of the Twin Cities, to support St. Paul.

MSA II.—The northeastern section of Minnesota, to support the Duluth Target area.

MSA III.—The northwestern section of Minnesota, to support the secondary target areas of Fargo-Moorhead, Grand Forks-East Grand Forks, and Manitoba, Winnipeg.

MSA IV and V.—Southwest, west, northwest and north of the Twin Cities, to support Minneapolis.

In these areas, communities with hospitals further distant than the cities selected for site-to-site relocation of target city hospitals are to plan for the expansion of hospital facilities. In MSA IV and MSA V they are expected to plan for 17,200 beds, the staffing pattern for which requires 950 physicians. There is need, also, for about 700 additional physicians to be assigned by Civil Defense to reinforce the supply of local physicians. Similar shortages are estimated for MSA I and MSA II. Such calculations confirm the estimated critical shortage of physicians that would occur after a mass attack on American target cities.

Surveys being made by nurses' organizations of registered nurses (active, part-time and retired) though still incomplete, would seem to show that an adequate number of R.N.'s will be available. Short courses (seven lessons of two hours) on atomic nursing are being given and will be available throughout the state. Eleven thousand five hundred registered nurses are required to staff a 350 CDEH (the equivalent of 70,000 beds).

Auxiliary nurses, students, licensed practical nurses, aides, and Red Cross home nursing trainees present a great problem of large deficiencies in numbers to meet the requirements of the Emergency Treatment Stations (ETS) and emergency hospitals. Every effort must be made to locate persons with auxiliary nursing training. The Red Cross is making every effort to step up the training in home nursing to meet this personnel deficiency. Junior and senior high school girls are a potential source of trainees in home nursing as well as college students in communities with colleges. Thirty five thousand auxiliary nurses are required to staff 350 emergency hospitals or 70,000 beds.

An outstanding development in the over-all Civil Defense organization for the target cities of Minneapolis and St. Paul is the UNICOM Operations Plan authorized by the Governor and Executive Council of Minnesota. It extends the authority and co-ordinating functions of the Civil Defense Director of St. Paul for a distance of 50 miles from an estimated inter-city aiming point over a half circle area (UNICOM DIVISION I), east of U.S. Highway 65. A similar half circle of a 50-mile radius west of U.S. Highway 65 (UNICOM DIVISION II) is under the direction of the Civil Defense Director of Minneapolis. The inner portion of the UNICOM area is the target area with a diameter of fifty miles allowing for a five mile error in the aiming point. The target area consists of four rings: The "A" ring of complete destruction has a radius of 5 to 7 miles; beyond this for 3 to 5 miles, the "B" ring presents such extensive damage that all building must be torn down; the "C" ring extends for an additional 3 to 5 miles in which practically all buildings must be vacated for repairs; in the "D" ring, damage will be of varying degrees but most buildings could be occupied while being repaired.

Extending for 25 miles past the target area is the assembly area of UNICOM—that of Division I extending 25 miles into Wisconsin. Most of the Emergency Treatment Stations (ETS) will be set up in the assembly area.

Under a 20 megaton surface burst attack, blast and thermal destruction may extend 11 or more miles from the point of detonation to doom all unprotected individuals. Casualty survivors may be found between the 11-mile and 17-mile radius —the outer portion of the "C" ring and the "D" ring. Such survivors may be exposed to initial and residual radiation, making it improbable that they will be rescued and receive medical care at the Emergency Treatment Stations within the time that attention could be life-saving. Beyond the area of blast and thermal damage, a megaton burst may produce serious radiation intensities for a few miles up-wind. Every effort should be made to provide radiation reduction protection. An average of nine hours and thirty minutes must elapse before radiation intensities decay to levels safe for continuous medical operations.

The Early Care of Bomb Casualties

Emergency Treatment Stations (ETS) replace the station group, which up until recently has been designated the casualty first aid system. Each ETS would be located on main Civil Defense evacuation highways as close to the damage area as permitted by radiation monitoring calculations. The selected locations are 30 to 50 miles from the zero point, but if indicated might be set up several miles closer in or moved out, if necessary, as it is a mobile facility. The function of the ETS is life saving medical and surgical care. It is a 128-litter hospital with provision for an additional 100 litters for holding. The basic equipment and supplies are the same as previously published (FCDA Technical Manual 11-1) for the casualty first aid services, and duplicates those of the thirty first aid units stored in Minnesota cities. The ETS does not have a clinical laboratory nor x-ray facilities. It is anticipated that an ETS will operate around the clock for at least one week and continue operation for a total of three weeks. Schools or other suitable buildings with 10,000 sq. ft. of floor space will be used. In certain favorable locations (adequate buildings, safety from fallout, et cetera), an ETS may later be converted into a 200-cot (or litter) definitive hospital, with the addition of more equipment. Associated with the ETS will be a first aid, receiving and sorting section, to

admit casualties requiring immediate care at the ETS; to sort and to arrange transportation to definitive hospitals of casualties requiring further care. Indicated first aid and other care will be instituted at the ETS.

The ETS staffing pattern includes eight physicians, six dentists and ten registered nurses, and the ETS for the Twin Cities will be located in twenty-three communities in Minnesota and Wisconsin. Most of the auxiliary nurses, other paramedical and maintenance personnel will be recruited, trained, and organized in the selected ETS communities. The medical, dental, and registered nurses personnel deficiencies will largely be supplied from suburbs close to the target areas if available. If not, such personnel will be sent forward from hospital cities 50 or more miles from the area of detonation.

Attached to each ETS are the Forward Aid Area rescue groups consisting of ninety-six litter-bearers (twenty-four teams of four) and twenty ambulance drivers—two to each vehicle—all trained in first aid. In case the selected ETS community does not have sufficient population to organize these groups, other communities on the same evacuation highways will organize the litter-bearer ambulance groups. It should be noted that to conserve professional workers for the staggering needs of mass casualties, no professionals, physicians, dentists, veterinarians or registered nurses will be assigned closer to the damage area than the ETS.

The blood program for Minnesota is making good progress with the plan of storing one year's supply in outlying hospitals to be replaced as used. An intensive training program of technicians is being organized. The estimated requirements for blood is 1500 units per 1000 casualties, during the first three weeks. FCDA, the Red Cross, and other blood banks are combining to produce 300,000 units of serum albumin per year for emergency.

Equipment and Supplies

FCDA has stored in forty warehouses, sufficient equipment and supplies to care for more than 3,500,000 casualties for three weeks and for more than a million non-casualties for a comparable period. Warehouses are located 30 to 100 miles from targets. Replenishment packs are being assembled—such as a three-weeks unit for the CDEH, 1000 casualty packs for the ETS, and 100 casualty packs suitable for civilian disasters. Recent plans are under way to assemble equipment for specialized surgery—dental, gastrointestinal, genito-urinary, cardio-thoracic and eye-ear-nose-throat, to meet the needs of long range care of our citizens. Improvisation must of necessity be of prime importance for Civil Defense Medical Care. Fortunately, drug stores, hardware and general stores, physicians and, where present, the hospital of a community, can provide enough equipment and supplies to treat at least 500 casualties. The concentration of most of our vulnerable medical equipment and supply industry is a matter of deep concern. Unless its dispersal can be accomplished, national stockpiling for the needs of a surviving population for 272 days post-attack is considered necessary by FCDA.

Dr. Max Van Sandt, Director of the Health Office, FCDA, stated at the eighth County Medical Societies Civil Defense Conference in Chicago, November 9-10, 1957:

"Under thermonuclear attack with ground burst weapons in the megaton range under present capabilities because of production vulnerability, minimum stockpiles and small inventories from production source to the user the recommended priority for medical care is:

1. Maintenance of health and production capability of the non-casualty survivors.

2. First aid and medical-surgical attention to the minimal (walking wounded) casualties to return them to productivity as soon as possible.

3. Medical care to women of child-bearing age and children.

4. Casualties that reach the medical channels.

"In conclusion, planning in the health field must provide for:

1. Programs that will reduce casualties and, where possible, reduce loss of existing facilities.

2. Medical care to casualties and emergency facilities to replace those estimated to be lost.

3. Medical care to the non-casualty survivors again in emergency facilities.

4. Public health protection in a sanitary environment that will allow our efforts toward recovery to function with a minimum loss of personnel to sickness and injury during the post-attack period.

5. Preparation of our citizens psychologically for the potential post-attack conditions which can be unleashed by an enemy capable of delivering such an attack.

Only in this way can we assure a minimum of health services to the survivors that will give our country a fighting chance to recover from the weight of an attack within the capability of our potential enemy."

Epilepsy in Childhood

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IN 1925 a definition for idiopathic or essential or cryptogenic or hereditary epilepsy was proposed by me, as follows: Idiopathic epilepsy is a chronic disease of the brain, characterized by periodically recurring convulsions; lapses, or abnormal mental states occurring in an individual with an inherited cerebral defect; but with no demonstrated pathologic lesion.[1]

Except for the amplifications resulting from progress in the study of this disease, the definition remains an all-inclusive description of this neurologic syndrome. The neurologists have challenged the term idiopathic, but whenever they wish to describe the disease, they use this or a similar term in quotation marks. Many investigators have challenged the hereditary origin of the disease. One in particular stated that the disease, epilepsy, is not inherited, only the tendency is. He also stated that epilepsy was not inherited any more than is diabetes. That is my contention. In my experience with this disease in children I have been able to obtain a positive family history in over 50 per cent of the cases. I have also been able to obtain abnormal electroencephalograms in at least 50 per cent of the near relatives of the patients with epilepsy.

The greatest contribution to the study of this disease came from Professor Hans Berger when he introduced the electroencephalograph in 1929.[2] Until that time, the diagnosis of idiopathic epilepsy was made on the history and a description of seizures, alone. There was no objective evidence to confirm the diagnosis. We were obliged to rely on the history as given, a description of the seizures, and the response to treatment. The diagnosis of idiopathic or cryptogenic epilepsy was made when all organic causes of the convulsions could be excluded. The electroencephalograph has made it possible to confirm the diagnosis and to distinguish the various manifestations and types of the disease. This is extremely important because of the modern advances in treatment.

Today, we do not treat the disease *per se*, rather we treat the specific manifestations of the disease and try to control the potential symptoms. However, the physician who is not familiar with the electroencephalograph must be advised of its limitations. It is a laboratory aid and not a diagnostic machine. Like the x-ray and the electrocardiograph, and all other laboratory aids, it may be of inestimable value in confirming a diagnosis with objective evidence; or, if it is negative, it must not be used to exclude a well-founded clinical diagnosis. The result of a test should never be allowed to confuse the issue. Unless the tracing is positive and definite, it should be interpreted without imagination.

Bucy of the Illinois Neurologic Institute warns his colleagues that, "However, the electroencephalograph is not, independently, a trustworthy diagnostic instrument. No one, by this means alone, can make a satisfactory diagnosis of epilepsy, a brain tumor, or a traumatic injury of the brain. The electroencephalograph by itself is also inadequate evidence on which to base treatment or to render a medical legal opinion. It is a matter of common experience that the information gained from electroencephalographic tracings may be grossly misleading and that great care must be exercised in correlating such records with all other clinical and laboratory data and in evaluating the electroencephalograph accordingly."[3] Boshes in a recent article called attention to the ridiculous extreme to which some of the electroencephalographers have gone in the interpretation of results using this experimental apparatus.[4]

In my definition, "convulsions" signifies the well-known and recognized major seizures of epilepsy. About one-half of the children have their onsets between eight and twelve years of age, usually with a major grand mal convulsion. One-half of these have a preliminary aura. These children seldom develop petit mal subsequently. One-half of the children have their onsets with petit mal or minor seizures which do not have an aura or loss of equilibrium. Most of these children have po-

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tential grand mal seizures and about half of them develop major seizures some time later. The "abnormal mental states" described in my definition are now understood to be either psychomotor epilepsy or hypothalamic syndrome epilepsy.[5] These conditions comprise a significant proportion of the behavior disorders in childhood, particularly between the ages of ten and eighteen years. They may or may not be associated with major convulsions. The diagnosis in psychomotor epilepsy may be confirmed when the electrogram shows positive negative spikes, particularly in the temporal lobes. The hypothalamic syndrome epilepsy may be confirmed when the electrogram shows fourteen and/or six-per-second positive spikes in the temporal lobe.[6]

The most effective treatment for epilepsy ever devised has been fasting and purging described by Hippocrates.[7] An attempt to reproduce the chemical effects of fasting resulted in the introduction of the ketogenic or high-fat diet.[8] This diet, like the diabetic diet, requires weighing or measuring of the food intake. It is no more undesirable or objectionable than the diabetic diet. Since it is aimed at the correction of an inherited serious disease which tends to be progressive and eventually produces deterioration of the brain, it is worth a fair trial. The effectiveness of the ketogenic diet can be determined within one week on a fast. If this fasting diet produces ketosis and a tendency to acidosis and does not control or prevent further seizures, the ketogenic diet will not be effective. The ketogenic diet eliminates the abnormalities in the electrogram.[9] It is effective in about 50 per cent of the cases and in all manifestations of the epilepsy syndrome, particularly petit mal and grand mal. If the diet is not practical or feasible, the second choice in treatment is, of course, drugs.

The present status of drug therapy was very well presented by Yahr and Merritt.[10] For the treatment of major convulsions of idiopathic epilepsy or of organic origin the drug of choice is phenobarbital U.S.P. This drug is universally available, relatively inexpensive, and harmless. The drug should be given to anticipate the expected seizures by several hours. The dosage should be increased until the seizures are under control unless undesirable side effects develop. The drug is available in capsules which provide a sustained and continuous release. If phenobarbital in adequate dosage is not effective or if it produces too much sedation or drowsiness, Methar-

butal or Gemonil® may be used. This barbiturate is an anticonvulsant with very little sedative effect and no other serious side effects. Phenobarbital is a drug which has diagnostic as well as therapeutic value. If the major convulsions cannot be controlled with an adequate and well-timed dose, the convulsions are probably of organic origin. If the convulsions are increased and misbehavior is aggravated, psychomotor, or hypothalamic syndrome epilepsy should be suspected.

Once the seizures are under control, the drug should be continued in the same dosage for at least one year and until a negative electrogram is obtained. Then the dosage may be tapered off gradually during the following year. The second drug of choice in the treatment of major convulsions is primadone or Mysoline®. This drug is relatively nontoxic and in small and increasing doses may be given to effectiveness usually without undesirable side effects. If neither phenobarbital nor Mysoline® are effective, perhaps a combination of the two will produce the desired results; if not, the next drug to be tried is phenacemide or Phenurone®. This is a toxic drug, but it is given as a calculated hazard in a serious or desperate situation. It is sometimes effective in the control of grand and petit mal seizures. When phenacemide is given, the blood count and the urine must be watched for toxic effects.

Dilantin® has not been a satisfactory drug in children. The therapeutic dose equals the toxic dose and almost always this drug produces disequilibrium and hypertrophy of the gums. A new hydantoin preparation, Peganone®, has now been introduced. I have used this drug for five years and have observed no serious toxic side effects. It is most effective in grand mal.

The diagnosis of petit mal or minor epilepsy should be confirmed if possible because petit mal *variant* seizures are usually of organic origin and do not respond well to the few drugs which are effective in the treatment of petit mal. The two effective drugs for petit mal are Tridione® and Paradione®. Whenever Tridione® or Paradione® are used, phenobarbital should be given concurrently because the diones may precipitate major seizures; also, the blood count should be followed regularly because of possible depression of the bone marrow. The "snow blindness" or visual disturbances which sometimes follow the use of these drugs is not serious and will clear when the drugs are discontinued. If the diones do not control

petit mal seizures, phenacemide should be given a trial. With this drug it is not necessary to add phenobarbital since phenacemide is an effective drug in the control of major seizures. Of the various other drugs advocated for the treatment of petit mal I have not found any consistently effective. A recent article reporting effective results with a new compound is open to question. The author admits that he has not effected changes in the electrogram. I have tried all the other drugs in adequate amounts for sufficiently long periods of time to be convinced of their inadequacy.

The treatment of psychomotor seizures and hypothalamic seizures presents a serious problem. Phenobarbital may be given for a diagnostic test. It usually aggravates or precipitates the misbehavior. The first drug which has ever been effective in the control of some of the children with psychomotor epilepsy is phenacemide. This is a toxic drug, but is well worth a trial. In older adolescents and adults it may precipitate a serious psychosis. In some patients it depresses the bone marrow, and in others it may produce liver damage. If the drug is not effective or if signs of toxicity appear, amphetamine (Benzedrine®) may be given a trial. It is a paradoxical fact that Benzedrine® sometimes has a sedative effect in these patients. So far, I have not found any of the antitension drugs of value in the control of behavior in patients with this type of epilepsy.

Surgery on the temporal lobe has not as yet produced any striking results. It is possible that decortication or ablation will help to control the behavior. However, in some reports ablation of the tip of the anterior temporal lobe in which the focus was located with the electroencephalograph has been followed by the appearance of a new focus in the opposite temporal lobe.

Summary

The treatment of epilepsy is a problem for the general practitioner and the pediatrist. The neurologist may be helpful in eliminating organic disease. It will be simpler for all of us if we confine the term "epilepsy" to the idiopathic type in which organic lesions have been excluded. It would be advisable to confine electroencephalography to the larger diagnostic centers, where the latest equipment and the best qualified technicians are available to produce records to be interpreted only by qualified electroencephalographers. There are a limited number of effective drugs available for the treatment of the various types of the epilepsy syndrome. These drugs should be used alone or, if necessary, in combination in an attempt to attain the desired results. The literature is full of reports of spectacular results obtained with new drugs. Many of these drugs have now been discontinued. Therefore, all reports must be carefully evaluated. In many cases the drug treatment resolves itself into a procedure of trial and error.

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HEART DISEASE AND HEART ATTACKS

Heart disease, now one of our greatest health problems, costs the U. S. government over $700 million annually. Loss in working time caused by the disease amounts to approximately $3 billion per year. The total annual outlay of the major sources of research support is currently estimated at $33,672,725.

Though heart attacks are often associated by laymen with over-exertion, they are far more likely to occur during periods of rest. Over half of the victims of coronary heart attacks are stricken while resting or sleeping. Less than 2 per cent are afflicted when engaging in "sports, running, lifting or moving a load."

—*Patterns of Disease*

Clinical-Pathological Conference

Sponsored by
The Minnesota Society
of Clinical Pathologists

CASE PRESENTATION—ST. MARY'S HOSPITAL (DULUTH)

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Clinical History.—This white, single, bricklayer, aged forty-three, was admitted on August 14, 1955, complaining of chest pain. This had begun five days previously; it was in the left chest and was aggravated by coughing and deep breathing. The pain was accompanied by persistent cough productive of a small amount of whitish sputum without blood. Weakness, dyspnea, chills and cold sweats also had been present most of the week. A 25-pound weight loss during the preceding three months had been associated with distinct anorexia.

A review of systems contributed no information other than that he had had three operations on his back five years previously following an injury and culminating in a spinal fusion. He had smoked one package of cigarettes per day for many years; a history of heavy alcoholic intake (at least one pint of whisky per day) was obtained, and alcoholic debauches lasting several days were common several times per month, and most recent immediately antedating the onset of his illness. No family history of tuberculosis could be obtained.

Examination revealed a temperature of 103° F., a pulse rate of 96 beats per minute, a respiratory rate of 24 per minute, and a blood pressure of 110 mm. of mercury systolic and 75 diastolic. The pupils were small, reacting slightly to light. The ocular fundi showed minimal sclerotic changes. The teeth were carious, with gingival infection; evidence of recent dental extractions was noted. Excursions of the left side of the chest were limited, and gross impairment of tactile and vocal fremitus was present over the left lower lung field. Numerous rales were present posteriorly on both sides, and bronchial breathing was noted in the left midlung field. The borders of the heart appeared within normal limits, and the rhythm was regular. The liver was barely palpable beneath the rib margin but was not tender. No other organs or masses were palpable in the abdomen, and tenderness was absent. The remainder of the examination contributed no positive information.

The leukocyte count was 19,350 cells per cubic millimeter (87 per cent neutrophils and 13 per cent lymphocytes), and the value for hemoglobin was 12 gm. per 100 ml. of blood; blood urea nitrogen measured 8 mg. per 100 ml.; the icterus index was 8.7 units. Other values were: serum sodium, 124 m.Eq. per liter; serum potassium, 3.3 m.Eq. per liter; serum albumin 3.3 gm. per 100 ml., and globulin, 2.9 gm.; thymol turbidity, 3.7 units; cephalin flocculation, 2 plus in twenty-four hours and 4 plus in forty-eight hours. A Kline test for syphilis gave negative results. The initial chest roentgenograms showed several areas of increased density in the right lung and a similar density involving the middle and lower portions of the left lung field. The sputum contained Gram-positive cocci in pairs on smears, while the culture showed alpha hemolytic streptococci predominating, with only a few pneumococci. Smears showed no acid-fast bacilli. Mantoux tests (dilutions of 1:10,000 and 1:1000) gave no reactions. An electrocardiogram was not abnormal. The urine had a specific gravity of 1.006, and was negative for albumin, sugar or abnormal microscopic elements.

Treatment with penicillin (600,000 units every six hours) and erythromycin (200 mg. every six-hours) was initiated. During the next twelve days, the patient showed continuous fever, usually between 103° and 105° F. Impairment of cerebration was manifested by recent memory loss, irrational behavior, slurred speech and episodes of frank confusion. The physical and radiologic signs in the lungs persisted and progressed. Blood-tinged sputum appeared. The addition of streptomycin and tetracycline failed to produce any permanent detectable change in the course of his illness, and on August 26, 1955, he was transferred to a tuberculosis sanatorium.

Upon arrival at the Sanatorium, the patient appeared moribund. A sister confirmed the previous history, adding the observation that the patient had had a nonproductive cough for eight or nine months that had become worse suddenly five days before hospitalization. Past employment had included jobs in the merchant marine, steel plants and construction crews. He was born in Minnesota and had left the state only for about three years while in the merchant marine during World War II, which included service in California and the Pacific Ocean.

Physical examination in the sanatorium showed signs of severe dehydration, with fever, toxicity and delirium. Radiologic changes in the chest were similar to those noted previously, although progression of involvement became apparent. The leukocyte count was 20,350, and the hemoglobin measured 11.7 grams. The urine showed a specific gravity of 1.025, 1 plus albumin, no sugar, 10 to 12 leukocytes per high-power microscopic field and occasional erythrocytes. The blood urea nitrogen was 19 mg. per 100 ml., and the serum chlorides were 83 m.Eq. per liter. Because of severe cyanosis, tracheotomy was performed and oxygen administered, with only moderate relief. Numerous smears of sputum showed no acid-fast bacilli, and cultures showed only coagulase-negative staphylococci. Cultures of sputum and tracheal washings for acid-fast bacilli and fungi were not completed before death, but malignant tumor cells were not demonstrable. Treatment with streptomycin, isoniazid and tetracycline, later supplemented with chloramphenicol and sulfadiazine, had no demonstrable effect. Fever continued, delirium passed into coma, cyanosis became constant, and the patient died on September 9, 1955, in an apparent state of respiratory insufficiency approximately one month after the acute onset of his illness.

From the files of the Department of Pathology, St. Mary's Hospital, Duluth, Minnesota.

Discussion

DR V. A. HARRINGTON:* The problem in this case is essentially that of a man with cough, weight loss, rapid progressive pulmonary consolidation, delirium and death. Since the roentgenograms show a con-

*From the Duluth Clinic.

siderable degree of pathologic changes, they will be presented first.

DR H. G. MOEHRING:* Several larger and smaller densities are obvious in each lung and are not segmentally arranged (Fig. 1). Abnormalities of the thoracic cage are not apparent. The later films show an increase in size of the densities, particularly in the right upper lung fields (Fig. 2). Small zones of decreased density also are noticeable within these densities, suggestive of cavitation, and a fluid level is distinct in some such areas. The last films show little functioning parenchyma. The lack of segmental arrangement of these densities suggests a blood-borne process that could be either inflammatory or neoplastic. Rapid progression makes inflammation more likely and the evidence of cavitation indicates necrosis.

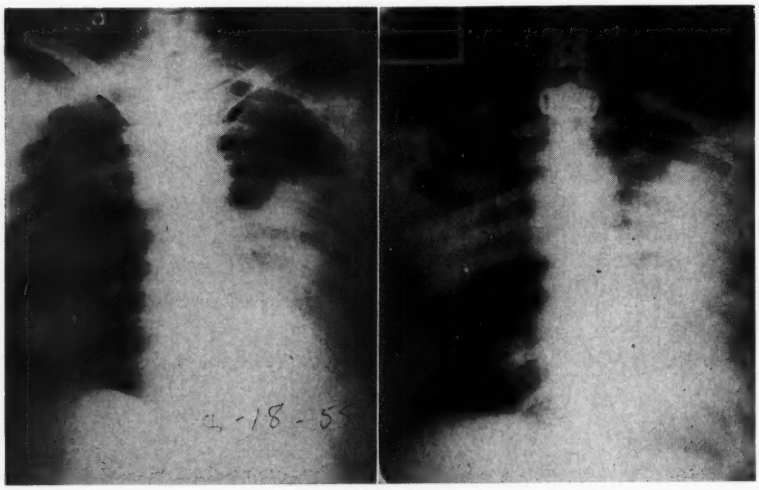


Fig. 1. *(Left)* Roentgenogram four days after admission. Extensive nodular involvement in both lungs is obvious.
Fig. 2. *(Right)* Roentgenogram seventeen days after admission. Pulmonary involvement is much more extensive.

DR. HARRINGTON: Of the malignant tumors, an extremely malignant lymphoblastoma is about the only primary type that would produce such a fulminating picture. The remarkable rapidity of the course, in addition to the fact that the disease remained limited to the chest, makes this diagnosis improbable. A shower of tumor emboli from a hypernephroma coincident with pulmonary infection conceivably could produce this picture, but such an improbable coincidence is unlikely. The clinical course is too rapid to be explained on the basis of metastatic carcinoma, so I consider that malignant tumors of any type can be excluded with reasonable safety.

Multiple pulmonary emboli must be considered but, if these huge densities on the roentgenogram represent infarcts, one would expect that one of the emboli would have caused earlier death. Chronic pulmonary embolization usually results in large numbers of tiny emboli, sufficient to produce pulmonary hypertension and death from failure of the right side of the heart.

Infection appears to be the only logical explanation of the pulmonary pathologic changes. It is inconceivable that this degree of cavitating pulmonary tuberculosis could exist without easily demonstrable acid-fast bacilli in the sputum. The increased leukocyte count, fever and early hypochloremia and hyponatremia all suggest an acute bacterial infection. Among organisms that commonly cause lung abscesses, *Klebsiella pneumonial* (Friedländer's bacillus), staphylococci and streptococci always must be kept in mind. Friedländer's pneumonia, however, usually is distinctly lobar in distribution, the bloody gelatinous sputum is characteristic, and organisms are abundant in the sputum. The acute form of this disease usually kills in less than a week. Streptococcic lung abscesses are usually due to group A, beta hemolytic streptococci, not the alpha hemolytic form isolated from this patient. Pneumococci, which causes 95 per cent of all pneumonias, were scarce in the original sputum smears; in addition, the distribution in the lung is atypical for this organism. Staphylococcal lung infections commonly produce necrosis and abscesses, and are often preceded by dental extractions, as in this patient.

A probable important feature in this patient is chronic alcoholism, for such patients are known to be susceptible to infection and resistant to treatment. In view of the fact that this patient's acute illness was preceded by dental extractions, it is tempting to postulate resulting bacteremia by any of the above-mentioned pyogenic bacteria. This may have been controlled partially by antibiotic therapy, as evidenced by a temporary decline in the temperature curve at that time. The subsequent increase in fever could be explained

*From the Duluth Clinic, Duluth, Minnesota.

by secondary invasion by an organism resistant to the antibiotics used. The coagulase-positive strain of staphylococci cultured from the sputum at this time is probably significant, and perhaps the organism was more

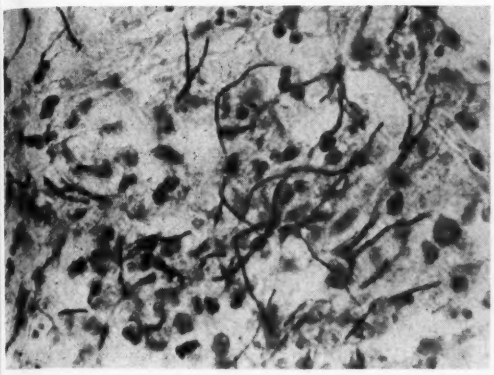


Fig. 3. Section of lung. Large numbers of organisms are apparent (Gram's stain; x900).

virulent than usual because of the deteriorated state of the patient resulting from alcoholism. Institution of chloramphenicol therapy (to which the organism had demonstrated sensitivity by *in vitro* tests) was again followed by a drop in the temperature curve, suggesting further that the staphylococci were playing a major role in the inflammatory process at this time and that sterilization of the pulmonary abscesses probably occurred. The final rise in temperature, which persisted to death, probably reflects invasion of a third organism, most likely a fungus.

A variety of fungi might be expected. *Candida albicans* is the most universally distributed member of the group. To indict it as a cause of pulmonary infection is a difficult clinical problem, one that is hazardous unless the fungus is grown in pure culture, since it is often found incidentally in sputum cultures. In this case, the wide range of antibiotics administered, as well as the fact that no other significant organism was cultured at this time, makes this a likely possibility. The cerebral changes described can be explained on the basis of toxicity from the overwhelming infection obviously present.

In summary, my reconstruction of the sequence of events would begin with dental extractions, bacteremia, diffuse pyogenic pneumonitis with multiple pulmonary abscesses and cavitation (staphylococcic), antibiotic sterilization and subsequent pulmonary invasion by a fungus (probably *Candida albicans*), progressing to a fatal outcome through pulmonary destruction and respiratory insufficiency.

Dr. Harrington's Diagnosis

Diffuse pulmonary moniliasis following staphylococcic pneumonitis caused by bacteremia induced by dental extractions.

Anatomic Diagnosis

Diffuse pulmonary nocardiosis.

DR. A. C. AUFDERHEIDE: The significant findings at necropsy were limited to the chest. A huge empyema was present in each pleural cavity, and fistulization into the chest wall had begun. Extension through the skin probably would have occurred within the next few days had the patient survived. The lungs each weighed 2400 grams. They were the seat of a very extensive purulent inflammatory process that involved every lobe of both lungs. In some areas consolidation was apparent, but in many other areas frank necrosis of pulmonary parenchyma had occurred, with the production of huge abscesses. Some of these had evacuated the exudate through large bronchi, with resultant cavitation. A large emphysematous bleb was present in the left apex. The remainder of the examination revealed no other organ involvement. Permission for examination of the head was refused, but involvement was not apparent in a portion of the lumbar spinal cord.

Microscopic examination revealed a simple purulent inflammation of the lungs entirely made up on neutrophils. No epithelioid cells, giant cells or other unusual features were noted. Extensive destruction of lung parenchyma, abscesses and cavity formation were obvious. Sections stained with hematoxylin and eosin revealed no etiologic agent. Acid-fast stains prepared in the usual manner showed no organisms. Gram's stains, however, showed huge numbers of gram-positive mycelial fragments characteristic of Nocardia (Fig. 3). Cultures of the lung revealed a pure growth of an aerobic mycelial fungus culturally and morphologically identical with *Nocardia asteroides*. The organism was pathogenic for guinea pigs. While it was not acid-fast when decolorized in the usual manner (with acid-alcohol), its acid-fast properties became apparent with more gentle decolorization (aqueous sufuric acid).

These mycelial fragments also were found in the sputum two days before death and were under study at the time the patient died. Cultures of the sputum obtained before death subsequently showed the same organism. All cultures and examinations for tubercle bacilli were negative. No other pyogenic organisms were demonstrated. Sensitivity studies showed this fungus to be resistant to erythromycin, penicillin and sulfadiazine; slight sensitivity was apparent to tetracycline and dihydrostreptomycin, while moderate sensitivity to chloramphenicol was noted.

Nocardiosis is an infection due to the fungus Nocardia sp. Although Nocardia is closely related morphologically and culturally to Actinomyces, it differs chiefly in that it is strictly aerobic and many species are acid-fast. Fragmentation of the finely branching mycelium into acid-fast rods frequently has resulted in an erroneous diagnosis of tuberculosis. The fungus is Gram-positive, cultures easily on standard media and can be separated from Actinomyces on the basis of its aerobic nature, acid-fast properties and pathogenicity

(Continued on Page 208)

Editorials

JOHN F. BRIGGS, M.D.
ARTHUR H. WELLS, M.D.
HENRY G. MOEHRING, M.D.

POST-SANATORIUM CARE OF TUBERCULOSIS

The markedly improved prognosis of the tuberculosis patient in the past decade has changed the attitude of the therapist in many ways. One danger is obvious. Undue optimism over present therapy can breed carelessness, neglect and eventual disappointment, either in the handling of an individual case or in a general program. Our new successes in tuberculosis therapy must not make us disregard careful and prolonged follow-up of every tuberculosis patient.

Post-sanatorium care starts with proper education of the patient while he is in the sanatorium, and is brought into sharp focus at the time of his discharge. To instruct the discharged patient to "see your family doctor regularly" and then close the sanatorium record was once fashionable though never medically wise. Today's patient should have on his discharge clear instructions regarding, and understanding of, the need for regular and faithful follow-up examinations to watch for return activity of his disease or tuberculosis complications. These instructions (a summary of which should not only be in the medical records but also available to his family physician and to the local Health Department) should include coverage of:

1. Daily schedule of rest and activity: Definite instructions should be given regarding the type and amount of daily activity permissible, including rehabilitation activities; the length of daily sleep and rest; possible need for recording of weight, temperature, respiratory or other complaints, or any other progress record the discharging physician may deem necessary. Such instructions should cover the interval until the first regular post-discharge examination (usually 6 to 12 weeks) and may be revised thereafter on each return.

2. Medication: If the patient is to continue on medication, directions regarding drug therapy must be clear and unequivocal as to dosage, duration of treatment, how and when to return for a drug refill, and the dangers both of neglect in taking medication regularly and of failure to report signs of drug reaction. To provide the patient with a printed form on which he is to record his actual drug intake day by day, for later review by his physician, may seem laborious but is well worthwhile.

3. Laboratory controls for the patient on drug therapy: None of the drugs used in tuberculosis therapy can be released to the outpatient with complete impunity or unconcern, for each can occasionally lead to serious reactions. Regular periodic blood counts (as for anemia due to para-aminosalicylic acid), liver function tests, and audiometric examinations (in long term streptomycin therapy), may detect early signs of damage and prevent serious developments. For the patient on well established therapy, post-sanatorium studies at three month intervals are generally sufficient.

4. Clinical, bacteriological and x-ray review: Such review should at first be frequent—say once in three months—with the interval gradually lengthened to one year as the patient's condition remains stable. A personal conference on each visit may be even more important than the routine chest film that is expected. The patient may by a question or two relieve himself of anxiety. The physician may detect signs of physical strain or of reactivation or complicating disease. His questions should relate not only to the chest but to any possible extrapulmonary foci as well. Thus a renal case may need cystoscopic re-evaluation or pyelography as well as or instead of chest x-ray.

Need for bacteriologic study must be carefully considered on each post-discharge examination. For the pulmonary case with expectoration, sputum microscopic *and* culture examinations at three month or longer intervals may suffice, but if sputum is scanty or non-obtainable, a series of three or more gastric specimens should be obtained periodically for culture or guinea pig study (microscopic study of gastric specimens is generally regarded as unreliable). Such series of gastric examinations are often advisable at three month intervals throughout the period of chemotherapy and again—as a test of effectiveness of therapy—at three months or even at six or twelve months after completion of the drug regimen. Again for the extrapulmonary case corresponding bacterial

examinations of urine or other excretion or drainage material may be in order. And finally, any hint of reactivation of a tuberculous focus even years after apparent control, calls for intensive bacteriologic re-study.

How long should clinical and x-ray follow-up be maintained? The known tuberculosis case should be re-examined at least annually throughout his remaining lifetime, for tuberculosis can and does reactivate after many years of apparent inactivity.

5. Liaison with auxiliary medical services: The discharging physician should also establish close co-operation between the patient, the sanatorium out-patient department, and various official agencies. Thus, the local health department and public health nurse need advice regarding the patient's discharge status, medications, home care, return to school or work activities, and follow-up schedule. The State Division of Vocational Rehabilitation may need repeated guidance on training and job placement for those patients requiring a change of work. And where family incompatibility, financial stringency, or emotional conflicts make personal adjustment critical, social service and welfare agencies may provide invaluable help.

As already implied, good post-sanatorium care of the tuberculous presupposes good indoctrination and training of the patient before his discharge. The well trained patient usually is a co-operative patient. He who leaves prematurely, with training broken and incomplete, is prone to become delinquent in follow-up, and so is more likely to become a public health menace if untraced.

For the tuberculosis patient discharged from the sanatorium following diagnostic study but with no present or recent activity demonstrated, clinical, x-ray and bacteriological follow-up may of course be modified accordingly—say routine annual recheck only.

One factor which unfortunately limits many post-sanatorium care programs is economic pressure. If both the community and the patient are limited economically, ideal follow-up becomes difficult indeed. Most communities in the United States today have the means to set up creditable programs, including free care for the economically straightened patient, if determined to do so. Certainly no area in Minnesota needs to be satisfied with inadequate tuberculosis follow-up.

R. W. Backus, M.D.

MEDICAL LIBRARIANSHIP: PRODUCT OF A NOBLE TRADITION

The doctor approached the reference desk. Eyes of the Egyptian clerk were question marks as they looked up at him from the scroll of a current best seller Grecian myth. The doctor wanted all the literature available on alopecia. There was a jangle of keys, the slow forced action on an unused lock, a door opening on rusting hinges. In the vault-like space, several pottery jars could be seen. From one of these, a roll was selected, dust rubbed from the writing. It was handed to the waiting doctor, who took it eagerly. At the one table in the poorly lit room, he unrolled his treasure. This was it—the papyrus on medicine, later to become the famous Ebers papyrus. It described all that was known about the diseases of the time with almost one thousand recipes for their cure. More wonderful still, some human anatomy had been included! The time was 1500 B.C.

The doctor again approaches the reference desk. He speaks distinctly into a microphone. Air vibrations activate the mechanism of a giant vaculux in front of him. He wants all the material available on Majocchi's disease. A red light flashes. There is the purr of machinery set in motion. The doctor looks at his watch. The light changes to green. Rolls of film strips, discs and microcards, done up in neat packets begin emerging from the pneumatic delivery tube. He inserts an attached card into a slot that automatically charges the materials and operates the contact which releases them to him. In a near-by sound proof, air-conditioned carrel, micro-readers are ready, not only to amplify the print, but to reproduce at the push of a lever any portion of the journals that he wishes to take with him. He sighs with satisfaction and again looks at his watch. The whole process had taken less than fifteen seconds. This is 2050 A.D.

Between the ages of papyri and of automation, the medical library evolved from the small collections of physicians to the multi-thousand volumes of books and journals which make up modern medical libraries as they are known today. What went into this evolution? Undoubtedly, in the beginning, the painstaking copying by hand of papyri and manuscripts preserved medical treasure for posterity. Early manuscripts were always compilations of much older works, which suggests the great antiquity of interest in medical writing. As

soon as printing was invented in 1450, medical literature literally tumbled from the presses. As early as 1686 a complaint appeared in the literature that "too many books are printed confusing and burdening the mind more than they instruct it." If the author of this remark lived now he could find listed in the latest edition of *World Medical Periodicals* 4,000 titles in medicine not including journals in fields related to medicine or from five to six thousand more periodicals containing scattered articles on the subject.

Understandably, physicians, themselves, may be considered the founders of both medical libraries and the profession of medical librarianship. Who better than they could appreciate the real values of healing buried in the scrolls and manuscripts of antiquity? And since, from earliest times, they represented the learned classes of society, it is logical that they were the ones to collect, interpret and preserve the books through which much of our culture is transmitted.

At first, the home or office of the physician was his library. As medical libraries became common in institutions, many physicians limited their library to a practical working collection and some, as a hobby or avocation, turned to the collections of rarities in the literature or to the searching out of papers and books in some highly specialized angle of medical learning. It can be stated with truth that there will never be an age in which physicians will not be leaders in their devotion to literature. Whether this love for books is natural or acquired, they are irrevocably committed to it. The fast moving pace of medical science has seen to this.

In addition to being the first to see the potentials in a collection of medical books, doctors have gone much further in their contributions to the medical library. Their far-sightedness early made them realize that if one physician's library was good, several combined ones would be better. And so they pooled their resources and formed society and institution libraries. Many hospitals owe their core collections to altruistic-minded staff members. Medical societies all over the world trace their origin to the same source.

In 1898, four American physicians met with four librarians and established what is known today as the Medical Library Association, one of the outstanding organizations in the current library world. The need for this enterprise was noted in an article written by C. D. Spivak in the *Philadelphia Medical Journal,* October, 1898, on "Medical Libraries of the United States." The author's statement, "There is no profession with so large and voluminous a literature and none in which its care is so neglected," summarized the thinking which gave birth to this project whose primary purpose was, and is, to encourage the formation of medical libraries.

Medical libraries in their cradle days were nurtured by the personal care of physicans. When the field became complex, physicians trained their secretaries to carry on while they retained the title of physician-librarian. In the meantime, the education of librarians was developing into a well defined science. In the first quarter of the twentieth century, physicians could begin to relinquish their work which they did so long and so well into the keeping of a profession descended from theirs and ancillary to them.

To Dr. John Shaw Billings, Surgeon General during the Civil War and later head librarian at the Library of the Surgeon General's Office, the forerunner of the National Library of Medicine in Washington, belongs the honor of the greatest contribution made by a single physician to the field of medical librarianship. His genius and foresight created one of the great reference tools for all times and is recognized as one of America's greatest contributions to medical science. This work, *The Index-Catalogue of the Library of the Surgeon-General's Office,* marked a goal in organized medical literature and was the forerunner of other great indexes, notably the *Index Medicus, The Quarterly Cumulative Index Medicus* and the *Current List of Medical Literature.*

Nor are doctors today less active or interested in the welfare of their medical libraries. Through membership dues, gifts and endowments, libraries, which are traditionally short of funds, are maintained according to high standards set up by the Medical Library Association and staffed by a growing number of qualified medical librarians.

Medical librarians, then, have a proud heritage. To their "founding fathers" can be traced ideals of dedication, of zeal for the furtherance and preservation of knowledge and a challenge of providing this, and future generations of physicians, with services abreast and in advance of the rapidly changing patterns in medical education and in research.

SISTER TERESA LOUISE, C.S.J.
Medical Librarian

TRENDS IN MEDICINE

As our medical antennae have become ever more sensitive to the causes of illness and accidents, we are aware that scarcely an illness lacks its emotional component. We have become correspondingly aware that more and more "organic illnesses" have roots in emotional causes. The "bottled-up" hypertensive, the ulcer patient who "swallows his anger," the attention getting asthmatic or arthritic, or the rejecting and rejected colitis problem are examples of emotionally caused illness. We are not yet willing to attribute all cause to emotions, for powerful still are bacteria, metabolic abnormalities, and new growths. More and more however we accept the mind and spirit as powerful etiologic agents in illness.

Stress is a popular word and a good one. It is stress of work, ambition, fear, and insecurity which we believe causes ulcers or colitis. It is the stress of self-containment and fear which may cause hypertension. Possibly it is the stress of conflict between ambition and accomplishment, between creative talent and expression, which causes arthritis, dermatitis, and allergies. Though there are many still unwilling to accept completely the idea that stress may be the principal cause of an illness, yet most physicians agree that it is a large and vital factor.

We should not eliminate stress from our lives even were it possible to do so, for stress is a necessary spur to achievement and essential to accomplishment. There is stress which is productive, and that which is futile. Stress may become distress. When accomplishment decreases under stress, when physical symptoms appear because of it, then we must decrease the load or run the risk of organic illness.

All of us know individuals whose days are crammed with excitement, problems, decisions, with haste and hurry, uncertainty and tension. Yet they seem serene, and they remain robust and well, carrying these burdens indefinitely. Stress is the ingredient in their lives which makes such activity possible and keeps them productive to the point of genius, but stress is not distressing. Others of our acquaintance buckle at the smallest decisions and are exhausted by the mildest deviation from routine. Major decisions and emotions are impossible for them. Distress is ailing them, and eventually will obtrude as an organic lesion susceptible to pathologists' classification.

The rigid and closed mind is also a product of stress. The insecurity of aloneness, the fear of non-conformity, dislike of the unknown are part causes of the rigid mind. That individual whose stand on any problem is completely predictable may be a great and consistent thinker, but more often he is one whose pattern is set and who fears because of distress to change it. We all know individuals who are young at eighty, and others who are aged at forty. Of course cerebral arteriosclerosis is often a major factor in this premature aging, but emotional approach to life is equally important. Faith, confidence, self-appraisal, and courage are the ingredients from which the Greeks propounded "Know thyself" as a guiding motto for life.

Faith is the factor least measurable in man's total health, yet perhaps most crucial. Faith has literally moved mountains, and there are thousands of patients to testify to the curative power of true faith. Man must have faith to live a full life and without faith life becomes meaningless. No physician has not witnessed the power of faith, and no physician can afford to ignore this tremendous aid in his therapy. We all want and need faith; it is part of the whole man, but often it must be learned.

Do I imply that the examining doctor should hold a religious catechism in his periodic examination? Certainly not. But neither do I believe that faith can be ignored as "belonging only to the church." Knowledge of an individual's faith or absence thereof is often of great help in care, and faith must neither be touted nor scorned by the physician.

CHARLES S. HOUSTON, M.D.
Aspen, Colorado

Second in a series of editorials on Trends in Medicine.

RESILIENT FLOORING IN THE DOCTOR'S OFFICE

For the doctor's office needing a "face-lifting," resilient flooring can make an important contribution, since the floor is such a conspicuous area in any decoration scheme.

Every kind of resilient flooring—linoleum and plastics in sheet form and the tile family of asphalt, vinyl-asbestos, rubber, cork, plastic, and special types—offers many, many patterns to fit any taste or decorative theme. The installation of

a new floor may be the only major change needed to transform an unrevamped office into a more attractive, more inviting space.

Besides decorative appeal, resilient flooring has other practical qualities that recommend it for use in doctors' offices. For one thing, it can be installed in hours—overnight, even—permitting renovation without the loss of a single working hour. Once the floor is installed, it's easy to keep clean and sanitary. Dirt can't stick to its smooth, lustrous surface, and a broom whisks it clean easily. Sweeping is the only care required daily, and an occasional scrubbing and waxing will help keep the floor like new.

The variety of colors and styles available with modern types of flooring is almost unlimited. Combinations of patterns can be used to add special effects to the basic design. For example, custom-designed insets can be laid into the floor in the form of "traffic lanes," a caduceus, or the name of a clinic.

Resilient flooring is quiet underfoot, for it cushions footsteps and reduces other noise that results from impact. This same quality of resilience makes the floor comfortable to walk upon. But for all its beauty, quiet and comfort, resilient flooring is durable and permanent when cemented properly to the subfloor. With the right sort of maintenance, it will give years of service without any appreciable loss of color and pattern design.

Before choosing a resilient floor for his office, the doctor should become acquainted with the types of flooring available.

Resilient flooring in sheet form offers the advantage of floors that are practically "seamless." There are two basic types.

Linoleum is probably the best-known and most widely used of all resilient flooring products, in both homes and commercial-institutional installations. With its coloring and patterns extending through to the backing, Linoleum is a long-wearing floor. It is grease-resistant and characterized by its smooth surface and even texture.

Plastic sheet flooring is one of the newest products in the flooring line. Ideal for highlighting modern, colorful decorative themes, it is made in a number of stylings. Quality plastic floors are resistant to abrasion and wear and will withstand the harmful effects of hot soapy water, alcohol, alkalis, dilute acids and most solvents.

Resilient tiles are being specified more than ever before. The ease of handling and replacement, coupled with unlimited design possibilities, has accounted largely for this increase in popularity.

Asphalt Tile, lowest in cost of all resilient floorings, is installable anywhere and is virtually unlimited in application. It is extremely durable, but is not quite so easy to maintain as most other types of quality resilient floors.

Vinyl-Asbestos Tile is fire-retardant and, like Asphalt Tile, can be installed even below grade-level. It is noted for the clear brilliance of its colors and may be safely used in areas subject to occasional spillage of acids.

Rubber Tile is a durable flooring with high resistance to wear and indentation. Its ability to cushion footsteps makes Rubber Tile particularly suitable where quiet is important.

Plastic Tile is a quality material recommended for all interiors where it is desirable to have the flooring match the architectural beauty of the room. It is highly stain-resistant, especially easy to keep clean, and installable in any location.

Cork Tile is most resilient—therefore quietest and most comfortable—of all floorings. It provides a distinctive appearance in areas where beauty and dignity are desired. However, it is not recommended for areas where excessive dirt and heavy foot traffic are likely to be encountered.

Custom Vinyl Cork Tile is a brand-new type of flooring that consists of Cork Tile with a layer of pure, clear vinyl plastic fused on as a wearing surface. Thus, it combines the beauty of natural cork with the durability and easy care requirements of plastics.

Linotile is especially processed for resistance to indentation and abrasion. It should not be confused with Linoleum cut into blocks. Tough and sturdy, Linotile is highly recommended for foyers and other "heavy-traffic" areas.

Linoleum Tile is Linoleum cut into squares to facilitate handling and installation. It is available in many of the same patterns as Linoleum sheet goods.

When selecting a resilient floor, it is well to remember that there is a right material available for every need. The doctor should study his own requirements, then consult a flooring dealer for help in picking the material that will give the most satisfactory service in the long run. Most flooring dealers and manufacturers have special facilities for assisting customers in choosing color schemes and designs.

C. Eugene Moore
Armstrong Cork Company

LIFE INSURANCE IN ESTATE PLANNING TODAY

Do You Have a Plan?

The young physician starting his practice should take the first steps to insure against two of the hazards that are common to everyone and concern us at every age level—*emergencies* and *premature death.*

A reserve fund for emergencies can be underwritten through disability income insurance or through a fund set aside from earnings or a combination of both.

Considering the hazard of premature death, Dr. B. L. Riese, addressing a recent graduating class of Northwestern University School of Medicine, told the young physicians that his classmates range in age from sixty-six to seventy-five years, that 67 per cent continue in active practice, 7 per cent are disabled, and that less than 30 per cent have been able to retire.

"If we may make a suggestion," Dr. Riese said, "to the young man starting out in practice, a suggestion born of long and bitter experience, it would be to buy all the life insurance they can afford to carry, in a sound company, and out of their surplus to buy bonds and stocks of basic industries, leaving the gold mines to the gamblers."

An essential element of a sound insurance program is that it is tailored to meet the specific needs of the individual. The young physician will find his need for insurance protection is the greatest when his funds available to buy it are the least adequate. So his insurance program is always going to include several compromises. His immediate need is for the most protection for the least cost. Thus his compromise may be for purchasing 5 or 10 year term insurance which can be converted to permanent insurance without physical examination. Another compromise might call for the purchase of family income or family maintenance type of life insurance.

Do You Have a Will?

Having made a start on the first two phases of his estate plan, the young physician should then complete the third phase; he should make a will. It has been said that a will is the most important document a man will ever sign, unless it is his application for a marriage license.

There is no other way in which a person can be sure that his estate, no matter how small, will be distributed according to his wishes at his death.

Do You Have an Interest in a Partnership?

It is often desirable to provide in advance for sale of a partner's interest to the surviving partners after his death. To provide funds for this purpose, insurance may be taken out on the life of each partner and made payable to the survivors. Difficult tax problems have been involved in such arrangements in the past—and there are new answers in the 1954 law.

Who should pay the premiums? Formerly it was thought advisable to avoid having any partner pay premiums on the policy insuring his life in order to bar the possibility of estate tax on the proceeds. Thus, for example, partner A would take out a policy insuring partner B and pay the premiums. B would take out and pay for a policy insuring A. Difficulty was encountered where A and B were of different ages, since the younger partner would have to pay higher premiums.

But the 1954 tax law removed this problem. It provides that the estate tax on insurance proceeds is not determined by who pays the premiums but by who owns the policy at the insured's death. If it is considered desirable, A can now pay the premiums on the policy insuring his own life; B the premiums on the policy insuring his life.

Should existing policies be used in setting up such an arrangement? It was formerly considered inadvisable to use existing policies to finance these cross-purchase agreements because of the possibility that the partner holding the transferred policy would have to pay income tax on receipt of the proceeds.

The 1954 law has solved this problem, too. It specifically exempts from income tax the proceeds of policies transferred to a partner of the insured.

This exemption is of special importance where there are more than two partners. If, for example, A, B and C each hold policies insuring the lives of his co-partners and A dies, B and C will want to acquire the policies held by A on their lives. This can now be done without fear of income tax.

It may be desirable to have the policies taken out by the partnership, rather than by the individual partners. This can simplify the arrangement where a large partnership is involved.

ALAN W. GILES
Northwestern Life Insurance Company

KUDOS FOR THE STAFF OF LIFE

Analyses of popular breads from thirteen countries of the world reveal that enriched bread made in the United States ranks high as the Staff of Life.*

In this study, carried out under the direction of Dr. Robert S. Harris, Head of the Department of Nutrition of the Department of Food Technology at the Massachusetts Institute of Technology, each bread sample was analyzed for moisture, fat, protein, carbohydrate, ash, calcium, phosphorus, iron, thiamine, riboflavin, niacin, pantothenic acid, folic acid, vitamin B_6, lysine, methionine, and tryptophan. The samples were ranked as a source of individual nutrients and the average rank taken as an indication of comparative nutritional value.

By this rating system a bread from Finland made from a combination of whole wheat and white flours plus a high level of nonfat dry milk placed first in nutritional value. American enriched bread ranked second.

The flour used to make our enriched bread is milled from a wheat higher in protein than that available in most countries. A typical formula for this bread includes, in addition to other ingredients, four pounds of nonfat dry milk and two and one-half pounds of compressed yeast for each hundred pounds of flour.

To this blend is added an enrichment wafer containing sufficient thiamine, riboflavin, niacin, and iron to permit a guaranteed level of these nutrients in the finished loaf. Minimum and maximum levels have been established by the Definitions and Standards of Identity for enriched bread promulgated by the Food and Drug Administration. These standards also limit the ingredients which may be used by the baker to known safe substances whose use does not conflict with the best interest of the consumer.

The high nutritional value of American bread as compared with the bread of the rest of the world must be credited to many groups: the Food and Nutrition Board of the National Research Council, the Council on Foods and Nutrition of the American Medical Association, the American Public Health Association, the Food and Drug Administration, and the milling and baking industries. It was through the efforts of these groups that the word "enriched" was officially endorsed at the National Nutrition Conference for Defense which met in Washington in 1941.

Unlike previous attempts to improve white bread's nutritional value, addition of the enriching ingredients did not change bread's sought-after flavor or character. It was this added value that made it possible for enriched bread to become a cornerstone of national health.

Although the wartime enrichment order was recalled after World War II, twenty-eight states have since passed enrichment laws of their own. Enrichment in the remaining states is a voluntary service of the baker.

AMERICAN INSTITUTE OF BAKING

*Included in this study were breads from: Australia, Austria, Cuba, Denmark, Finland, France, Germany, Italy, Norway, Philippines, Sweden, Switzerland, and the United States.

CLINICAL-PATHOLOGIC CONFERENCE

(Continued from Page 201)

for guinea pigs. While Actinomyces usually demonstrates susceptibility to penicillin, the sensitivity of Nocardia to antibiotics varies, usually being greatest to the sulfonamides.

The method of human infection is speculative at present. Clinically, the infection commonly is either a chronic subcutaneous abscess (mycetoma) or a deep-seated infection (pulmonary or cerebral, or both). Pulmonary nocardiosis may mimic the various forms of tuberculosis and, for previously mentioned reasons, the fungus infection may be misdiagnosed and treated as tuberculosis. It has been estimated that as many as 10 per cent of patients hospitalized in some tuberculosis sanatoria are actually suffering from nocardiosis. The fungus demonstrates a predilection for the central nervous system, with fatal cerebral abscesses reported in patients whose lungs revealed no detectable evidence of infection at necropsy. Detection and diagnosis depend on suspicion. Treatment is by chemotherapy or the use of antibiotics as indicated by sensitivity studies.

DR. HARRINGTON: In retrospect, it should be pointed out that the organism causing nocardiosis is one fungus that explains adequately all phases of this case, and it is unlikely that it was a secondary infection.

It is unfortunate that the brain could not have been examined, since a significant number of patients with nocardiosis have involvement of the central nervous system.

Initial signs of lymphosarcoma in children may include petechiae, pallor, ecchymoses, enlarged lymph nodes, splenomegaly, hepatomegaly, skin nodules, weakness or anorexia.

MINNESOTA BLUE CROSS-BLUE SHIELD

Both the amount Minnesota Blue Shield paid physicians during 1957 for care of participant subscribers, and the number of doctors' services for which Blue Shield provided benefits were over 22 per cent greater than during 1956. Since the number of participant subscribers increased approximately six per cent over the number of subscribers enrolled at the end of 1956, the percentage increase in payment and services is primarily the result of expanded Blue Shield coverage and greater utilization.

Blue Shield provided benefits of $8,473,555 during 1957 for physicians' services rendered participant subscribers. This figure is equal to average monthly payments of over $706,000, and is more than $1,500,000 greater than the total amount paid by Blue Shield for care of subscribers during 1956. Blue Shield provided benefits of $6,919,348 in 1956 for physicians' services to participant subscribers.

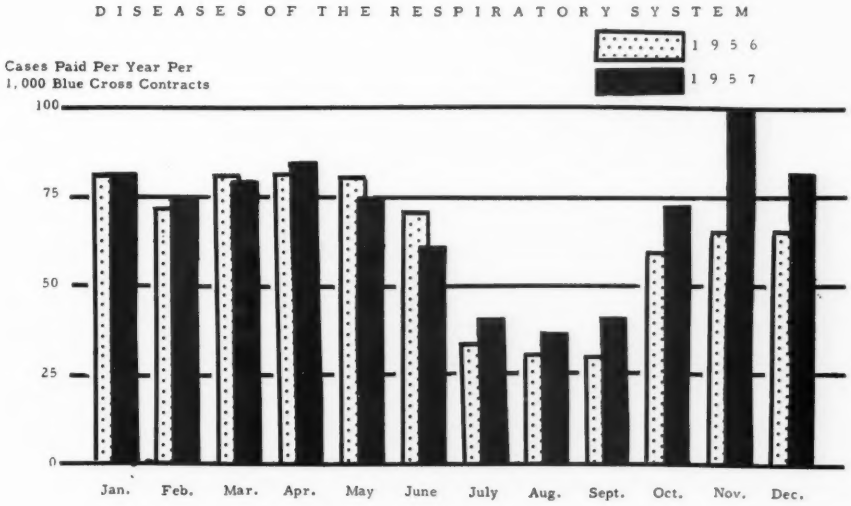
The number of physicians' services for which Blue Shield provided benefits during 1957 was 307,171, exceeding by more than 56,000 the number of doctors' services for which Blue Shield provided benefits during 1956.

Blue Shield participant subscribers numbered 869,985 as of December 31, 1957, or 46,883 participant subscribers more than the number enrolled as of the same date in 1956.

Payments in the form of hospital benefits for Minnesota Blue Cross participant subscribers reached an all time high of over $28,500,000 for the year ending December 31, 1957.

This all time high in benefits was provided to 202,704 participant Blue Cross subscribers for 1,233, 492 days of hospital care, reflecting an incidence rate of one case paid for every two Blue Cross contracts protected during 1957. This is a five per cent increase in frequency over 1956.

The increase in usage of Blue Cross benefits is attributable most importantly to a four per cent increase in the number of cases paid for conditions related to pregnancy, a six per cent increase in benefits paid for accident cases, and an eleven per cent increase in the number of patients hospitalized for diseases of the respiratory system.



Data collected by the Public Health Service indicates the peak in the recent Asian influenza outbreak was reached in the week ending November 2nd. The number of Blue Cross subscribers hospitalized for diseases of the respiratory system during the last quarter of the year 1957 follows the nationwide trend recorded for Asian influenza.

Respiratory cases took an abnormal upward trend during the last quarter of 1957 as compared to the previous year. The upward trend was largely due to an increase in the number of Blue Cross patients hospitalized for medical care such as influenza, pneumonia and upper respiratory infections. During the last quarter of 1957, 6,454 Blue Cross members and dependents received medical care in hospitals for respiratory diseases, compared to 3,636 during the same period of the preceding year.

Accident cases sent more Blue Cross subscribers to the hospital during 1957 than any illness or disease. Over 34,000 persons received Blue

(Continued on Page A-60)

President's Letter

CIVIL DEFENSE AND CIVILIAN DISASTER

One Sunday afternoon, in 1939 or 1940, a tornado struck Anoka, Minnesota. There were a few people killed and quite a number injured. In a few minutes, a call went out over the radio for doctors to come to Anoka. Those who thought they could help started on their way. The rest of us did not happen to have the radio on. Half an hour or so later, the announcer asked that no more doctors come to the scene of the tornado; there were too many doctors and, besides, the roads were so filled with sightseers that the ambulances and service crews could hardly get into the town, and the disaster was not as bad as it seemed at first. In other words, planning was absent, the improvised arrangements were more or less hysterical and were finally interfered with by the morbidly curious who could only hinder what progress was being made.

Over the years since that time, we have slowly recognized that care of the injured in a small calamity requires forethought and planning just as it does in a disaster or catastrophe. However, as our population increases and the concentration of people becomes greater, the possibility of more injuries occurring simultaneously increases and the need for disaster planning becomes more urgent. Now, practically every hospital and almost every staff has an outline for procedure in case of a sudden influx of casualties. In fact, soon a disaster plan will be one of the requirements for hospital accreditation.

The usual pattern is selection of an area in the hospital as a receiving center, assignment of the staff to various teams, such as shock, transfusion, surgery, fractures, and psychiatric care. What is just as important is planning to bring in the laboratory staff for blood typing, transfusion, blood expanders, et cetera; the supply department for extra beds, blankets, and bedpans; and the kitchen and maintenance help simply to feed and house the whole group, staff as well as patients, and, equally important, enough administrative and clerical help so we know who is injured and where they are.

Now, if we enlarge the "ordinary" civilian disaster almost immeasurably, we can begin to conceive of the planning for civil defense. As Dr. Carl Waldron has done elsewhere in this issue, try to imagine an enormous disaster—a bomb which can not simply blow up a few buildings but which can wipe out the whole of Minneapolis and St. Paul with one blast. The bomb has a force of 20 megatons, in other words, the equivalent of 20 million tons of TNT. The Civil Defense planners, the Federal Civil Defense Administration, are working with the idea that such a bomb could be delivered but that there would be from two to six hours' warning. During that time, according to the present plan, the target areas would be evacuated. All roads would be made one way (out) and a speed of 30 miles an hour maintained, which makes such an operation imaginable. There would, then, be an enormous problem in caring for the healthy or the routinely sick, not to mention casualties. At first, the only concern was for care of the injured, and depots of supplies have been provided in northern Iowa and various

parts of Minnesota to set up emergency treatment stations and emergency hospitals. The ordinary health care and sanitation for such a displaced population is now recognized as a really major problem, and when it comes, as we hope it never will, this may be the answer to the survival of the nation.

In the planning for such a major "national emergency" (an understatement, but the only words that seem to fit), it is recognized that the physicians of the target areas may be decimated and certainly will be displaced. Therefore, the burden of organized care will fall on the medical and paramedical professions in parts of the state away from the targets. The actual planning is being done by the physicians engaged full time in community care, the state and local health officers, and by such dedicated men as Dr. Carl Waldron of Minneapolis, who has spent almost full time in this field for about four years; Dr. Hans Schwyzer of St. Paul, who has given generously recently; and Drs. Edwin G. Benjamin and Nathan C. Plimpton, who have spent part time for twelve years and have a large experience in Minneapolis problems. Others have contributed greatly in St. Paul, Duluth and other areas around the state. However, it is recognized that the actual work will be done by physicians and others miles away from the cities.

The Federal Civil Defense Administration has made a contract with the American Medical Association for planning medical care in a national emergency. For various reasons, one of which is the relatively advanced planning in this state, the Twin City area has been selected for a pilot study. To make this survey valuable, the aid and co-operation of all the doctors is needed, especially those away from the cities. In the cities, the surviving doctors will simply be told where to go, but in the surrounding towns, the survey and plans will include not only medical abilities but people and supplies: nurses—active and inactive, dentists, veterinarians, people to carry stretchers, to set up beds, to cook, and to keep records. Supplies will be surveyed: supplies in doctors' offices, in hospitals, in drug stores, in wholesale houses and warehouses, even in hardware and furniture stores, besides the more obvious blood bank supplies.

In the care of the health of the "surviving population," the key person is the doctor in the area not hit by a bomb. The association of these key people is the State Medical Association. Therefore, the State Medical Association, through its president, urges your full co-operation and your earnest help. The Association office will do its best to keep you informed.

Because of the key position of the medical profession in care of the health of survivors and casualties, our part is being carefully planned. At the same time, we recognize that other people, other professions, are striving to increase understanding between nations, to prevent the bomb's ever being dropped. The best civil defense is the brotherhood of man and is the ideal toward which the world must grow. The role of medicine, however, until that ideal is attained, is to plan and to know the technique of survival in catastrophe, and to repair and to care for the people involved.

Horatio B. Sweetser

President, Minnesota State Medical Association

Medical Economics

Edited by the
Committee on Medical Economics,
Minnesota State Medical Association
George Earl, M.D., Chairman

BEHAVIORAL SCIENCE NEEDS STRESSED

Powerful development of behavioral science—"the science of man"—to bolster national defense, secure the peace, and strengthen the United States in many ways, has been recommended by an informal study committee of fifteen persons.

The recommendations were made in a 7,000 word report which suggested establishment of an advisory panel of behavioral scientists to work with James Killian, Jr., science advisor to the president. The report also called for provision of greater public and private funds to stimulate research in the various sciences of man.

Chairman of the committee was Dr. James G. Miller, director, Mental Health Research Institute at the University of Michigan.

VA DOCTOR PAY HIKE ASKED

The Veterans Administration is asking congress for funds to grant an average 7 per cent increase to its doctors. The increasing difficulty of hiring and retaining physicians is the reason given for the request.

According to the VA, doctors in private practice make more money and even those on salaries in miscellaneous jobs at a greater advantage with their fringe benefits as well as fatter pay envelopes. Congress is expected to grant the request.

REORGANIZATION WOULD AFFECT GOVERNMENT MEDICAL CARE PROGRAM

Passage of a bill which would revolutionize the government's medical care mechanism is being urged by the Citizen's Committee for the Hover Report.

Observers feel that effects of the bill would be felt not only at the bureaucratic level but in the office of every physician who ever treats a Federal beneficiary or who possesses hospital privileges or who is subject to military obligation or who prescribes drugs—in short, all of them.

The bill, if adopted, would establish a Federal Advisory Council of Health, directly responsible to the President. Congress is expected to give the bill careful consideration before approving additional funds for hospital construction and doctor training programs.

WORKMEN'S COMPENSATION NEEDS OVERHAUL—MEANY

A special conference of labor representatives, April 15-17, has been called by George Meany, president of the AFL-CIO, to discuss overhaul of workmen's compensation laws.

Meany's statement announcing the conference said, in part,

"The advance of medical knowledge concerning occupational diseases has not been reflected in the adaptation of state workmen's compensation laws to protect workers occupationally injured.

On-the-job safety programs have been neglected and, with the exception of a few states, only token consideration, if any, has been provided for the physical, mental, and vocational rehabilitation of the injured worker."

AMA PROPOSES MODEL LAW TO CUT POISON DEATHS

A model law which would require precautionary labeling of hazardous substances in commercial, household, and industrial chemical products has been proposed by the AMA committee on toxology.

The proposed legislation was announced recently by Mr. Bernard E. Conley, Ph.D., secretary of the AMA committee, before a section of the New York Bar Association. Mr. Conley told the law group that the proposed legislation is intended as a model for uniform laws to require declaration of hazardous ingredients and warning statements on the label and in the accompanying literature of chemical products in the home and elsewhere.

Mr. Conley pointed out that the law is directed against those hazardous substances defined as toxic, irritating, sensitizing, corrosive, inflammable, explosive, or radioactive under customary or reasonably anticipated conditions of handling and use.

The law, as drafted by the AMA committee

headed by Dr. Torald Sollmann, Cleveland, Ohio, would:

—Require the labeling of all chemical products containing hazardous substances which are not now regulated.

—Require the same labeling standards to apply to chemicals for export as those for domestic consumption, thereby obviating the common complaint that less-than-standard products are sold to foreign customers.

—Prohibit re-use of food and drug containers bearing their original labels.

—Require identification and warnings for strongly sensitizing chemicals which cause allergic or inflammatory reactions in living tissue on contact.

The committee's work had strong support not only from the chemical industry but also from the National Drug Trade Conference and the American Public Health Association.

QUACKERY CRACKDOWN IS ON THE MARCH IN ILLINOIS

The State of Illinois has recently taken a number of important steps to curtail the activities of quacks and unlicensed practitioners in the healing arts. Penalties for violators have been increased and examinations have been made more difficult. Provisions have been made for the publication and widespread distribution of an annual roster listing all licensed physicians. Also included in the publications will be up-to-date information on suspended and revoked licenses.

Members of the Minnesota State Medical Association are urged to be alert to possible influx of unqualified practitioners driven out of Illinois by the new regulations.

GP HEAD BLASTS COMPULSORY HEALTH INSURANCE

Politicians campaigning for compulsory health insurance might as well try to pass a law against Asian influenza. Dr. Malcom E. Phelps, El Reno, Oklahoma, head of the American Academy of General Practice stated recently:

"For more than twenty years," Dr. Phelps said, "an assortment of misguided politicians have tried to buy votes by offering 'free' medical care plans. They consistently fail to point out that medical care is like any other commodity; you get just what you pay for; no more.

"I don't care whether you call it socialized medicine or compulsory health insurance. There's no difference between the two. The most important consideration, as far as I'm concerned, is the health of my patients. They deserve the best medical care available and I don't want them misled by the wild promises of politicians who don't know the first thing about modern medical care.

"Any one who has talked to British doctors knows exactly what I mean, "Dr. Phelps added.

"In Britain, the government levies a fat tax and then tells the people that they are entitled to 'free' medical care. This is absurd. Under the British National Health Insurance plan, the doctor averages about four minutes per patient. The patient stops being a person and becomes a number on a government file folder, buried under a pile of complicated forms and health insurance regulations.

"Doctors have been accused of being against health and welfare plans and it's time someone set the record straight. We're not against anything that means better medical care. But we know, better than anyone in Washington, that you can't legislate good medical care any more than you can pass a law against Asian influenza.

"Some of the political pressure groups talk about a shortage of doctors. I'd like to remind them that the nation's medical schools have set eight new enrollment records in the last eight years. I'd also like to tell them that a great many doctors would retire rather than practice 'bargain basement' medicine under compulsory health insurance.

"If the American people want a shabby health care system, all they have to do is turn it over to professional politicians," Dr. Phelps concluded.

The American Academy of General Practice, with headquarters in Kansas City, Missouri, is the nation's second oldest medical association representing 23,000 family doctors.

SOCIAL SECURITY DISABILITY CHECKS NEAR $10 MILLION EACH MONTH

During the first six months of operation of its disability payments program, the Social Security Administration estimates that approximately 131,000 persons are now receiving payments. This total is expected to increase to nearly 200,000 by July of this year. The Social Security Administration points out that the average payments to the disabled are $72.24 a month. This compares with the national average of around $65 for all other retired.

This is explained in part by the fact that (a) the national average takes in many older persons who were not fully employed in previous years and (b) wages have gone up since the 1930s and early 40s. The disabled covered, on the other hand, come more recently from the labor market.

On the basis of 200,000 on the rolls next year and assuming the average monthly payment is unchanged (which is unlikely), the Disability Trust Fund will be paying out at the annual rate of nearly $175 million. SSA estimates that the fund had $525 million in it as of September. This is derived from the ¼ of 1 per cent payroll tax increase that went into effect January, 1957. Note: At the time of the hearings on the disability proposal, HEW Secretary Folsom pointed out that the program for the first full year would cost close to 200 million, rising to around $900 million in 1980.

"MD INTERNATIONAL" WELL RECEIVED IN MINNESOTA

The American Medical Association-Smith, Kline and French TV show, "MD International," was big news in the medical field recently.

Many at AMA headquarters who saw the one hour show over the NBC-TV network on Thursday evening, January 23, rated it the best of the March of Medicine series.

The *Chicago Tribune* critic said the fine show renewed his faith in the future of television.

"It contained scenes of such pathos, high purpose, and elemental humanity that it must be ranked high on the list of TV documentary films," the *Tribune* writer said. "Rave notices" also appeared in many other papers throughout the country.

This was the filmed story of American doctors in eight locations. The seven men crew made the 34,000 mile trek in 81 days—to Korea, Hong Kong, Borneo, Burma, Lebanon, Nepal, Ethiopia, and India. The film has a "cast of thousands"—and not one was an "extra."

The show was carried on 148 NBC network TV stations. In Minnesota "MD International" was aired over KSTP-TV, Twin Cities; KROC-TV, Rochester; and KDAL-TV, Duluth. Early estimates indicate that the presentation was viewed by 20 million persons.

Vice President Richard M. Nixon introduced the program.

The popular March of Medicine series has been a public service function of the AMA and Smith, Kline & French since 1952.

STUDIES ON PLASMIN: FACTORS IN LYSIS OF THROMBI

(Continued from Page 191)

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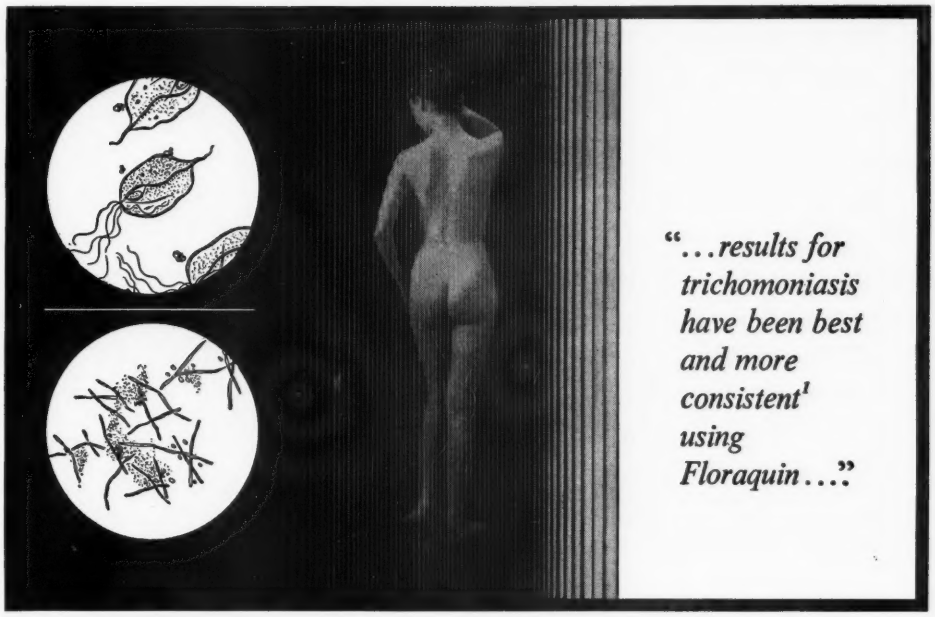

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SEARLE

In Memoriam

RICHARD B. HULLSIEK

Dr. Richard B. Hullsiek, chief medical officer of the regional veterans administration office at Fort Snelling, died February 2, 1957, of a heart attack, at the age of fifty-nine.

He had been in charge of the VA medical clinic at Fort Snelling since 1946. He lived on the post.

Dr. Hullsiek, a lifelong Twin Cities resident, attended Macalester College, St. Paul, and graduated from University of Minnesota Medical School in 1924.

A private practitioner in St. Paul until 1940, Dr. Hullsiek then entered the army as a medical officer. He served in Europe with the rank of colonel during World War II. He also was a veteran of World War I.

Dr. Hullsiek was a member of the American Medical Association, Minnesota State Medical Association, Ramsey County Medical Society and Medical Forum.

Survivors include his wife, Stella; a son, Richard, Jr., Bloomington; a daughter, Mrs. Donald P. Moffitt, Minneapolis, a brother, Dr. Harold E. Hullsiek, St. Paul, and a sister, Mrs. Henry Koll, Chicago.

JULIUS JOHNSON

Dr. Julius Johnson, Minneapolis physician for more than fifty years, died February 8, 1958. He was eighty years old. His specialty was Neurology and Psychiatry.

A native of Sacred Heart, Minnesota, he received his preliminary education in the rural schools of that community and at St. Cloud State Teachers College.

His medical education was obtained at the Minneapolis College of Physicians.

He interned for one year at St. Barnabas Hospital in Minneapolis. His post graduate work included four months at Harvard Medical School.

Dr. Johnson served on the staffs of Swedish, St. Barnabas, Fairview, St. Andrews, Deaconess and Glenwood hospitals.

He was a life member of the Minnesota State Medical Association, a member of Hennepin County Medical Society and the American Medical Association. Other memberships held by Dr. Johnson included: the American Psychiatric Association, Minnesota Society of Neurology and Psychiatry and Phi Rho Sigma medical fraternity.

Dr. Johnson also belonged to Wesley Methodist church, Masonic lodge 19, Scottish Rite and Zuhrah temple of the Shrine.

Survivors included his wife, Bess R., a daughter, Mrs. H. G. Creel, Palos Park, Illinois.

(Continued on Page A-48)

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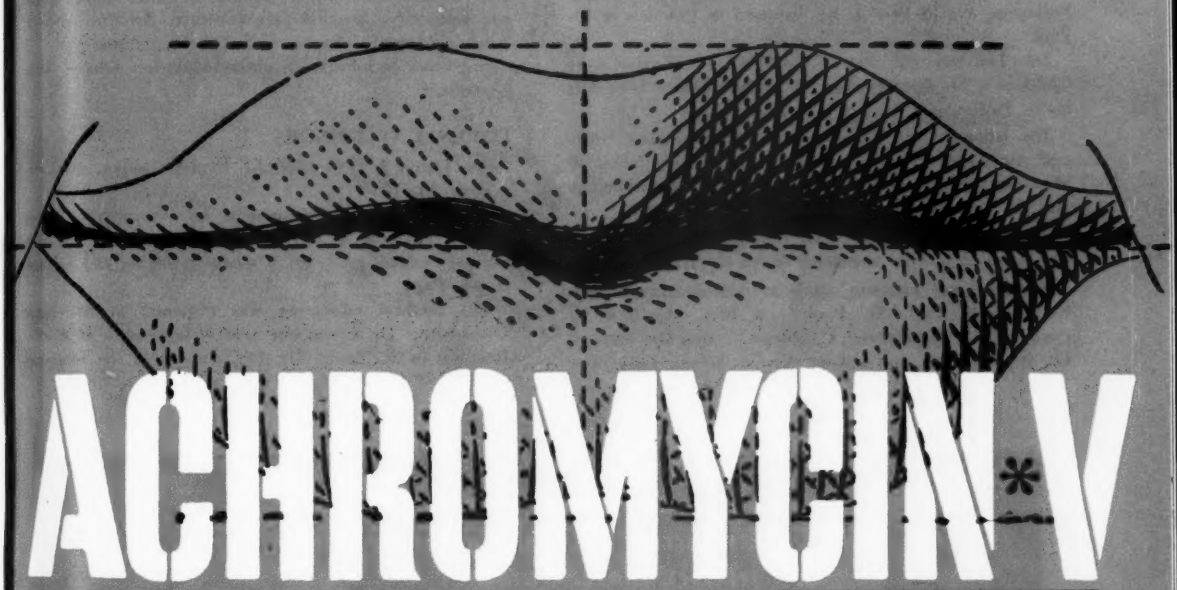

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PEARL RIVER, NEW YORK

(Continued from Page A-46)

RICHARD O. LEAVENWORTH

Dr. Richard O. Leavenworth, St. Paul, former chief of the eye, ear, nose and throat department at Ancker Hospital in St. Paul, and former clinical instructor at the University of Minnesota, died January 29, 1958. He was sixty-eight years old.

He was a graduate of the University of Minnesota. Dr. Leavenworth took post graduate work at a number of American and foreign universities.

Prior to fourteen months service in World War I in France, he practiced medicine in Glencoe, Minnesota. Following World War I, he returned to practice in St. Paul.

Dr. Leavenworth was a member of the staff's at Children's, St. Joseph's, St. Luke's and Miller Hospitals in St. Paul.

He belonged to Ramsey County, Minnesota State and American Medical Associations and was a fellow of Minnesota and American Academies of Ophthalmology and Otolaryngology.

A fellow also of American College of Surgeons, he was certified by the American Board of Ophthalmology.

Survivors are his wife, Geneva; two daughters, Mrs. Edmund A. Post, St. Paul, and Mrs. Harrison H. Cochran, Jr., San Gabriel, California; a son, Dr. Richard O., Jr., Excelsior, and a sister, Louise, Schenectady, New York.

CARL M. OBERG

Dr. Carl M. Oberg, Minneapolis, died February 6, 1958. He was eighty-one years of age. His specialty was eye, ear, nose and throat. He was born in Sweden in 1876.

Dr. Oberg was a graduate of the University of Minnesota Medical School, class of 1899.

He was a life member of the Minnesota State Medical Association, a member of the fifty year club, and the Hennepin County Medical Society.

He also belonged to the American Academy of Opthalmology and Otorhinolaryngology, Deaconess hospital medical and surgical society, Phi Rho Sigma medical fraternity, Swedish art institute, Swedish society, Anchor Masonic chapter and Zuhrah temple.

Survivors include a daughter, Margaret Oberg, Minneapolis.

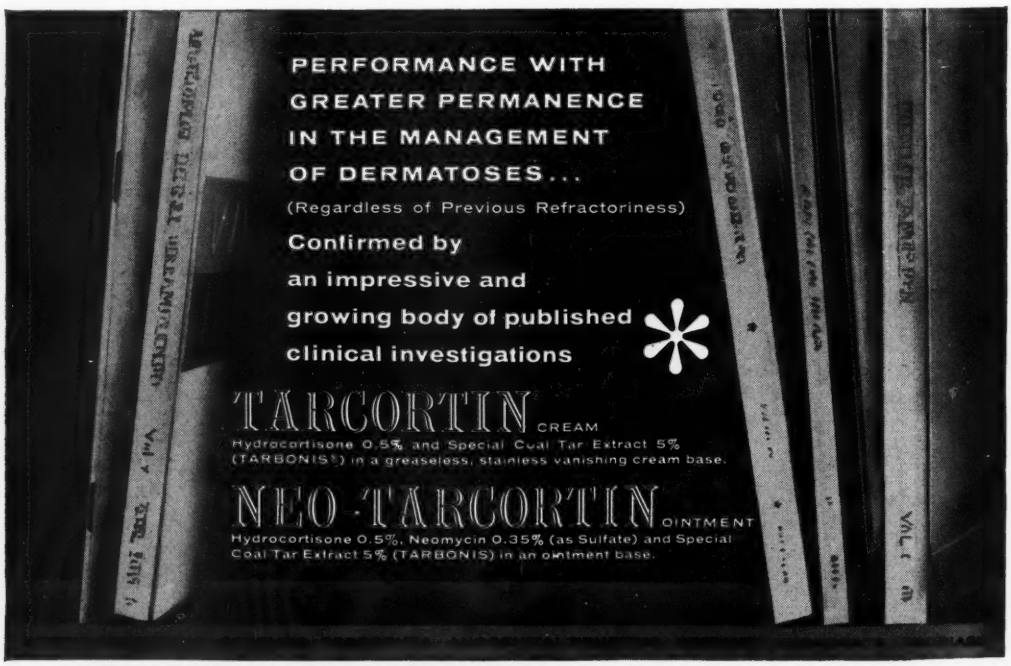
LOREN J. O'CONNOR

Dr. Loren J. O'Connor, St. Paul physician, died December 14, 1957.

Born in Delano, Minnesota, he was fifty-six years old at the time of his death. He received his preliminary education at St. Thomas Academy and College in St. Paul.

His medical education was obtained at St. Louis University. He served one year of internship at Ancker Hospital in St. Paul. Dr. O'Connor held the following

(Continued on Page A-50)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IN THE MANAGEMENT
OF DERMATOSES...
(Regardless of Previous Refractoriness)
Confirmed by
an impressive and
growing body of published
clinical investigations
TARCORTIN CREAM
Hydrocortisone 0.5% and Special Coal Tar Extract 5%
(TARBONIS*) in a greaseless, stainless vanishing cream base.
NEO-TARCORTIN OINTMENT
Hydrocortisone 0.5%, Neomycin 0.35% (as Sulfate) and Special
Coal Tar Extract 5% (TARBONIS) in an ointment base.

* J.A.M.A. *166*:158,1958; Welsh, A.L. and Ede, M. "...*prompt remissions of...acute phases.*" with TARCORTIN

R&C REED & CARNRICK / Jersey City 6, New Jersey

* 1. Clyman, S. G.: Postgrad. Med. *21*:309, 1957.
2. Bleiberg, J.: J. M. Soc. New Jersey *53*:37, 1956.
3. Abrams, B. P., and Shaw, C.: Clin. Med. *3*:839, 1956.
4. Welsh, A. L., and Ede, M.: Ohio State M. J. *50*:837, 1954.
5. Bleiberg, J.: Am. Practitioner *8*:1404, 1957.

See anybody here you know, Doctor?

I'm just too much

AMPLUS®
for sound obesity management
dextro-amphetamine plus vitamins and minerals

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STIMAVITE®
stimulates appetite and growth
vitamins B_1, B_6, B_{12}, C and L-lysine

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a nutritional buildup for the OB patient

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one capsule a day, for all treatable anemias

With my anemia, I'll never make it up that high

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when more than a hematinic is indicated

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... solve their problems with a nutrition product from ROERIG

New York 17, New York
Division, Chas. Pfizer & Co., Inc.

(Continued from Page A-48)

positions and affiliations: Associate Member of the Minnesota State Medical Association, a member of the Ramsey County Medical Society and the American Medical Association. He also served on the staffs of St. Joseph's, Bethesda and Midway Hospitals.

HARRIS RAYMOND SUTTON

Dr. Harris Raymond Sutton, sixty-nine, of Hoffman, died January 16, 1958, at the Douglas County Hospital in Alexandria. His death followed a two month illness caused by lung cancer.

A native of Prior Lake, Minnesota, he received his elementary education at Windom Institute at Montevideo. He took his A.B. degree at the University of Minnesota in 1912 and in 1916 he was awarded the Doctor of Medicine degree. He had his interne experience in Ancker Hospital, St. Paul, and from 1917 to 1920 he served in the United States Navy Medical Corps.

Dr. Sutton was a member of Nu Sigma Nu Medical Fraternity, Phoenix Lodge A.F. & A.M. No. 313 and the Hoffman Post of the American Legion. At the time of his death he was chairman of the board of education of Independent Consolidated School District No. 265, Hoffman, a post he had held for many years. He had also served several terms as village mayor and council member. He was a member of the Park Region District and County Medical Society, an active member of the Minnesota State Medical Association and the American Medical Association.

On May 31 last year Dr. Sutton's many years of medical practice and public service were recognized at a special Dr. Sutton Day observance at the Hoffman school auditorium. The event was under sponsorship of several Hoffman and Kensington organizations.

Survivors are his wife, Clara, two sons, Harley M. of Minneapolis and Forest of St. Paul; one daughter, Mrs. Richard (Shirley) Davis of LaCrosse, Wisconsin. He also leaves three grandchildren, Joni Gayne Sutton, Scott Davis and Richard Davis; two sisters, Maude L. Sutton of Batavia, Illinois, Cora S. Castle of San Francisco, California, and one brother, Leonard Sutton of St. Paul.

CLARENCE E. WILLCUTT

Dr. Clarence E. Willcutt died January 8, 1958, in Phoenix, Arizona. He was seventy-four years of age.

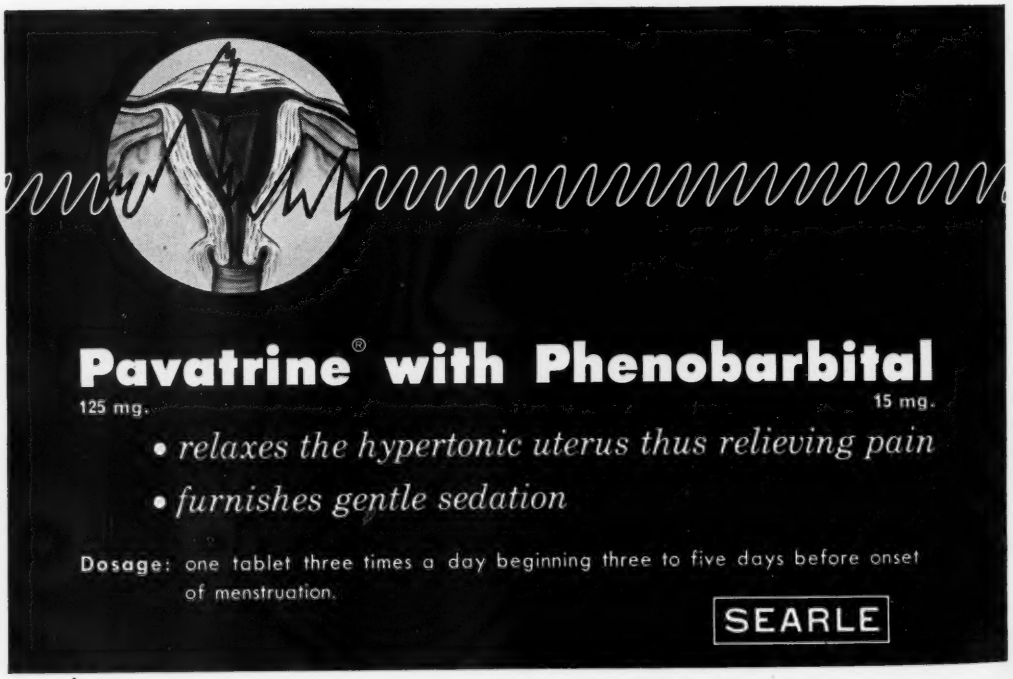
A former Minneapolis Obstetrician and Gynecologist, Dr. Willcutt had resided in Phoenix, Arizona, for a number of years because of ill health.

He was born in Ida County, Iowa. His medical training was obtained at the State University of Iowa.

Dr. Willcutt was an associate member of the Minnesota State Medical Association and a member of Hennepin County Medical Society.

Survivors include his wife, three sons, Robert of Minneapolis, Clarence of Minneapolis and Charles of Chicago; two sisters, Ethel Willcutt of Minneapolis, and Mrs. J. A. Gray of Iowa.

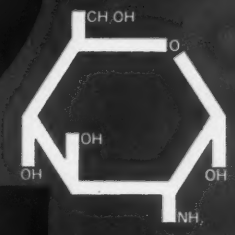
in dysmenorrhea


Pavatrine® with Phenobarbital
125 mg.
15 mg.
• relaxes the hypertonic uterus thus relieving pain
• furnishes gentle sedation
Dosage: one tablet three times a day beginning three to five days before onset of menstruation.
SEARLE

Three advantages of glucosamine-potentiated tetracycline:

1 ***Highest, fastest tetracycline blood levels,*** with glucosamine enhancement. A screening program involving 84 possible adjuvants, multiple four-way crossover tests, 30,000 blood level determinations and more than 100,000 assays proved glucosamine to be the enhancing agent of choice.

2 ***Greatest consistency of higher tetracycline blood levels*** Not only does glucosamine considerably increase antibiotic blood levels faster, but it produces these higher blood levels more consistently as shown by extensive crossover tests.



3 ***Achieved with the physiologic advantages of glucosamine,*** a normal human metabolite. Glucosamine, found widely in the body, is nontoxic and does not irritate the gastrointestinal tract; there is evidence that glucosamine may favorably influence the bacterial flora of the intestine. Further, it is sodium free and releases only four calories of energy per gram.

in new well-tolerated

The most widely prescribed broad-spectrum antibiotic now potentiated with glucosamine, the enhancing agent of choice

COSA-TETRACYN

GLUCOSAMINE-POTENTIATED TETRACYCLINE

Capsules, 250 mg., 125 mg.
Half strength (125 mg. capsules) for long-term indications or pediatric use.

Pfizer Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N.Y.

Correspondence

KENNY INSTITUTE CLEFT PALATE CLINIC

Many months of planning and work by leaders in the various disciplines and agencies concerned with the care and treatment of patients suffering from cleft lip and/or cleft palate has culminated in the establishment and opening of a cleft palate diagnostic and evaluation clinic at the Elizabeth Kenny Institute, Minneapolis. This clinic, staffed by a rotating group of particularly qualified professional people representing the various disciplines involved in the long term management of persons having clefts, was made possible through a grant by the Kenny Foundation. Services of this group are available on an outpatient basis to all physicians seeing or treating cleft lip and/or cleft palate.

This clinic was predicated on the concept that the physical, mental and social potentials of persons suffering from cleft palates are best realized by a blending of all the professional disciplines that might be involved and that the over-all, long range program habilitation is most effectively carried out by the patient's own private physician and dentist. Thus, all referrals to this clinic must be made by the patient's physician. Recommendations and plans for therapy originating from this clinic will be forwarded to the referring physician as well as an invitation for the physician to participate in the formulation of these plans.

A complete study, including cephalograms, intra-oral radiographs, study models, intra-oral and extra-oral photographs, audiograms, speech analysis and a medical social service study will be made routinely. If desirable, further laboratory analysis, psychological evaluation and vocational guidance will be provided. The group organized to carry out this program includes a pediatrician, plastic surgeon, dentist, orthodontist, prosthodontist, psychologist, speech pathologist, medical social worker and, if necessary, an otolaryngologist and vocational counselor. Several complete panels have been organized to allow for a rotation of members throughout the year.

A complete analysis of the various studies made by each discipline involved will be formulated during a panel session into a long-range program of therapy. Referring physicians and other persons playing a role in the complete habilitation will be provided with all the available information. All persons involved in the care and treatment of the patient will be informed of the time the patient will be seen by the panel and invited to participate. All actual treatment will be conducted under the direction of the patient's own physician or dentist, not by members of the panel unless the panel member happens to be the patient's referring doctor.

Further information and referrals may be made by contacting the Kenny Institute Cleft Palate Clinic, Dr. Ralph B. Kersten, Coordinator, 1800 Chicago Avenue South, Minneapolis, Minnesota.

CERVICAL CARCINOMA

In a three-year study of cervical carcinoma, also at Parkland Memorial Hospital, Drs. M. A. Litton and P. O'B. Montgomery found evidence to support the assumption that social and environmental factors are important causes of cervical cancer. Early marriage, early childbirth and non-circumcision appeared to be significant factors in the patients studied.—*Dallas Medical Journal,* December, 1957.

and inflammation
with **BUFFERIN®**
IN ARTHRITIS

salicylate benefits with minimal salicylate drawbacks

Rapid and prolonged relief—with less intolerance. The analgesic and specific anti-inflammatory action of BUFFERIN helps reduce pain and joint edema—comfortably. BUFFERIN caused no gastric distress in 70 per cent of hospitalized arthritics with proved intolerance to aspirin. (Arthritics are at least 3 to 10 times as intolerant to straight aspirin as the general population.[1])

No sodium accumulation. Because BUFFERIN is sodium free, massive dosage for prolonged periods will not cause sodium accumulation or edema, even in cardiovascular cases.

Each *sodium-free* BUFFERIN tablet contains acetylsalicylic acid, 5 grains, and the antacids magnesium carbonate and aluminum glycinate.

Reference: 1. J.A.M.A. 158:386 (June 4) 1955.

ANOTHER FINE PRODUCT OF BRISTOL-MYERS

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"Since we've had him on NEOHYDRIN he can walk without dyspnea. I wouldn't have believed it possible a month ago."

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Meetings and Announcements

STATE

MINNESOTA STATE MEDICAL ASSOCIATION, 105th annual meeting, Minneapolis, May 22, 23 and 24, 1958. Business sessions and exhibits, Minneapolis Auditorium. Headquarters, Leamington Hotel.

Minnesota Surgical Society, spring meeting, Rochester, Minnesota, May 9, 1958. O. H. Beahrs, M.D., Secretary, Rochester, Minnesota.

NATIONAL

Aero Medical Association, annual meeting, Statler Hotel, Washington, D. C., March 24-26, 1958.

American Congress of Physical Medicine and Rehabbilitation, 36th annual scientific and clinical session, Bellevue-Stratford Hotel, Philadelphia, August 24-29, 1958.

American Gastroenterological Association, 59th annual meeting, Washington, D. C., May 30-31, 1958. H. M. Pollard, M.D., Secretary-General, University Hospital, Ann Arbor, Michigan.

National Health Forum, Sheraton Hotel, Philadelphia, Pennsylvania, March 18-20, 1958.

National Industrial Health Conference, 13th session, in Atlantic City, New Jersey, April 19-25, 1958.

INTERNATIONAL

Fifth International Congress on Diseases of the Chest, sponsored by American College of Chest Physicians, Tokyo, Japan, September 7-11, 1958.

Fifth International Congress of Internal Medicine, Philadelphia, Pennsylvania, April 24-26, 1958. Edward R. Loveland, Secretary-General, 4200 Pine Street, Philadelphia 4, Pennsylvania.

International Society of Internal Medicine, Fifth International Congress of Internal Medicine, Philadelphia, Pennsylvania, April 24-26, 1958. Edward R. Loveland, Secretary-General, 4200 Pine Street, Philadelphia 4, Pennsylvania.

Third International Congress of Allergy, sponsored by International Association of Allergology and French Allergy Association, Paris, France, October 19-26, 1958.

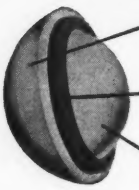
World Congress of Gastroenterology, Washington, D. C., May 25-31, 1958. H. M. Pollard, M.D., Secretary-General, University Hospital, Ann Arbor, Michigan.

(Continued on Page A-56)

NEW *"flavor-timed" dual-action*
CORONARY VASODILATOR

Dilcoron TRADEMARK

ORAL (tablet swallowed whole)
for dependable prophylaxis
SUBLINGUAL-ORAL
for immediate and sustained relief
of **ANGINA PECTORIS**



NITROGLYCERIN—
0.4 mg. (1/150 grain)—acts quickly

CITRUS "FLAVOR-TIMER"—
signals patient when to swallow

PENTAERYTHRITOL TETRANITRATE—
15 mg. (1/4 grain)—prolongs action

For continuing prophylaxis patient swallows the entire Dilcoron tablet.
Average prophylactic dose:
1 tablet four times daily.
Therapeutic dose:
1 tablet held under the tongue until citrus flavor disappears, then swallowed.

Bottles of 100.

Winthrop LABORATORIES NEW YORK 18, N. Y.

If
Monilial overgrowth
is a factor

Achrostatin* V

TETRACYCLINE (PHOSPHATE-BUFFERED) AND NYSTATIN

Combines ACHROMYCIN V with NYSTATIN

ACHROSTATIN V combines ACHROMYCIN† V ... the new rapid-acting oral form of ACHROMYCIN† Tetracycline ... noted for its outstanding effectiveness against more than 30 different infections ... and NYSTATIN ... the antifungal specific. ACHROSTATIN V provides particularly effective therapy for those patients prone to monilial overgrowth during a protracted course of antibiotic treatment.

SUPPLIED:

CAPSULES contain 250 mg. tetracycline HCl equivalent (phosphate-buffered) and 250,000 units Nystatin. ORAL SUSPENSION (cherry-mint flavored). Each 5 cc. teaspoonful contains 125 mg. tetracycline HCl equivalent (phosphate-buffered) and 125,000 units Nystatin.

DOSAGE:

Basic oral dosage (6-7 mg. per lb. body weight per day) in the average adult is 4 capsules or 8 tsp. of ACHROSTATIN V per day, equivalent to 1 Gm. of ACHROMYCIN V.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N. Y.

*Trademark †Reg. U. S. Pat. Off.

Lederle

(Continued from Page A-54)

POSTGRADUATE COURSES ANNOUNCED

New York University-Bellevue Medical Center's Post-Graduate Medical School offers the following postgraduate courses to be given or started during the month of May, 1958:

Symposium on Dermatology and Syphilology (for Dermatologists)—May 19 through 23

A full-time course of five days' duration. Given under the direction of Professor Marion B. Sulzberger. Maximum class 20. Tuition: $100.

Cardiology—May 5 through 23

A full-time, three weeks' comprehensive course. Given under the direction of Dr. Charles A. Poindexter. Maximum class 40. Tuition: $250.

Advanced Course in Urology (for Specialists)—May 12 through 23

A full-time course of two weeks' duration. Given under the direction of Professor Robert S. Hotchkiss. Tuition: $175.00.

OPHTHALMOLOGY FELLOWSHIP ESTABLISHED

The Department of Ophthalmology of the New York University-Bellevue Medical Center announces the establishment of the Daniel B. Kirby Fellowship for Research in Ophthalmology.

To be eligible for this award, the candidate must have had a thorough grounding in ophthalmology, roughly equivalent to a three-year residency, or should have acquired equivalent competence in a basic field related to ophthalmology.

Fellows will be expected to continue work on basic problems in such fields as ocular chemistry, physiology, pathology, or experimental surgery, and will be supplied laboratory space and facilities in the Center. The initial appointment will be for one year at a basic stipend of $7,000, and will be subject to renewal for two additional years.

SUMMER CAMP FOR DIABETIC CHILDREN

The summer camp for diabetic children will be conducted for the tenth year under the auspices of the Chicago Diabetes Association from July 20 through August 10, at Holiday Home, Lake Geneva, Wisconsin. Boys and girls from eight through fourteen years of age are eligible.

AURORA MEDICAL STUDENT WINS RURAL SCHOLARSHIP

Mr. Edward S. Peterka, of Aurora, has been awarded the 1957 Rural Medical Scholarship sponsored annually by the Minnesota State Medical Association.

The recipient is a freshman in the University of Minnesota Medical School. He is a graduate of the Aurora Public Schools and attended Virginia Junior College prior to enrolling in the University of Minnesota.

In 1946, when he was a senior in high school, his

(Continued on Page A-58)

New STEELINE Pediatric Table

Eases the burden of the physician's daily work

Includes built-in tare balance scale, built-in measuring rod, foam rubber cushion and electrical outlets with cord and plug—there are no accessories to buy. Top quality construction features include all-welded steel body, two roomy drawers and a large open compartment with shelf, providing easy, unhampered access to instruments and supplies. Front edge is protected from wear by a stainless steel baffle plate. Despite the fact that this new table has been designed to provide the physician with the best modern equipment, efficient modern production methods in our own factory permit us to keep the price well below that of comparable models. Write today for complete information.

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STOP respiratory congestion orally

relief in minutes..lasts for hours

In the common cold, nasal allergies, sinusitis, and postnasal drip, one timed-release Triaminic tablet brings welcome relief of symptoms *in minutes*. Running noses stop, clogged noses open—and *stay* open for 6 to 8 hours. The patient can breathe again.

With *topical* decongestants, "unfortunately, the period of decongestion is often followed by a phase of secondary reaction during which the congestion may be equal to, if not greater than, the original condition. . . ."* The patient then must reapply the medication and the vicious cycle is repeated, resulting in local overtreatment, pathological changes in nasal mucosa, and frequently "nose drop addiction."

Triaminic does not cause secondary congestion, eliminates local overtreatment and consequent nasal pathology.

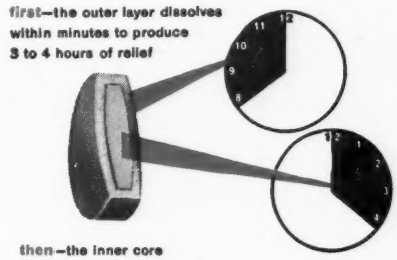
*Morrison, L. F.: Arch. Otolaryng. 59:48-53 (Jan.) 1954.

Each double-dose "timed-release" TRIAMINIC *Tablet contains:*

Phenylpropanolamine hydrochloride	50 mg.
Pyrilamine maleate	25 mg.
Pheniramine maleate	25 mg.

Dosage: 1 tablet in the morning, afternoon, and in the evening if needed.

Each double-dose "timed-release" tablet keeps nasal passages clear for 6 to 8 hours—provides "around-the-clock" freedom from congestion on just three tablets a day


first—the outer layer dissolves within minutes to produce 3 to 4 hours of relief
then—the inner core disintegrates to give 3 to 4 more hours of relief

Also available: Triaminic Syrup, for children and those adults who prefer a liquid medication.

Triaminic®

"timed-release" tablets

STOP *running noses...* *and open stuffed noses orally*

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska • Peterborough, Canada

For active mothers-to-be

Ulvical® (Ulmer) assures these modern ladies-in-waiting of a generous amount of iron and calcium plus the recognized prenatal vitamins . . . in a small tablet . . . especially designed for rapid assimilation and easy toleration.

For maximal utilization . . . timed release of these essentials is accomplished by special coatings controlled to dissolve at the pH of the stomach, duodenum and jejunum.

Important, too, calcium pyrophosphate contains larger amounts of elementary calcium which is quickly metabolized to increase plasma blood levels. Leg cramps are quickly relieved; small daily doses sustain this relief.

Each tablet contains:

Calcium Pyrophosphate (Ca 150 mg., P 120 mg.), 7½ gr.
Ferrous Sulfate USP (Fe 38 mg.) 3 gr. 3.8 M.D.R.
Vitamin A (Ester) 1500 USP Units ⅜ M.D.R.
Vitamin D (Irradiated Ergosterol) 200 USP Units ½ M.D.R.
Thiamine Mononitrate (B_1) 1 mg. 1 M.D.R.
Riboflavin (B_2).... 2 mg. 2 M.D.R.
Ascorbic Acid (C) 16.66 mg. ½ M.D.R.
Vitamin E.....2.2 I.U.* (from d alpha tocopheryl acetate N.F.)

M. D. R. — Minimum Daily Requirement. *M.D.R. not established.
Dose: One or two tablets three times a day.

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THE ULMER PHARMACAL COMPANY
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(Continued from Page A-56)

father died. Following the death of his father, he spent the next two years working to support his widowed mother and a younger sister. In spite of his role as a breadwinner, he was able to save funds for his future medical education. His military experience includes two years with the United States Army in Korea.

The rural scholarship award was established six years ago by the Association to assist worthy and outstanding students, meet the high cost of medical education and to insure a supply of physicians in non-metropolitan Minnesota communities.

Dr. Richard Engwall, the first person to receive this scholarship, is now a practicing physician in Ivanhoe, Minnesota. Other scholarship recipients, now attending the University of Minnesota Medical School include: Leland Christenson, Marshall; Myron Doebler, Princeton; Carl E. Christenson, Stanchfield; and Vincent R. Hunt, Anoka.

CRIPPLED CHILDREN SERVICES CLINIC SCHEDULE, SPRING OF 1958

St. Cloud—March 11-12—Bethlehem Lutheran Church —E. Stearns, Benton, Sherburne, So. Mille Lacs

Grand Rapids — March 12-13 — Court House — Itasca, Cass (Remer and Longville area)

Cloquet — March 19 — National Guard Armory — Pine and Carlton

Albert Lea—April 2—Freeborn

Brainerd — April 8 — First Methodist Church — Aitkin, Crow Wing, Cass, No. Todd, Wadena and No. Mille Lacs

Hibbing — April 10-11 — National Guard Armory — St. Louis, W. Range

Detroit Lakes—April 23—Armory—Clay, Becker, Mahnomen

Thief River Falls — April 29-30 — Trinity Lutheran Church—Kittson, Marshall, Pennington, Red Lake, Roseau

Gaylord—April 30—City Hall—Brown, Carver, Scott, McLeod, Nicollet, Sibley, LeSueur

Duluth—May 7—United Baptist Church—Lake, Cook, So. St. Louis

Fergus Falls—May 8—Armory—Ottertail, Wilkin

International Falls—May 16—Koochiching, Lake of the Woods

Faribault—May 21—St. Luke's Evangelical Church—Dakota, Goodhue, Rice, Steele

Worthington—May 24—Cottonwood, Jackson, Murray, Nobles, Pipestone, Rock

Morris—June 3—High School—Swift, Stevens

All new patients are requested to bring written referrals from their family physician.

All patients should have appointments arranged locally.

Note: Gillette State Hospital patients will not be attending any orthopedic field clinics.

(Continued on Page A-60)

IN ALL DIARRHEAS . . . REGARDLESS OF ETIOLOGY

comprehensive control with CREMOMYCIN®

SULFASUXIDINE* PECTIN-KAOLIN-NEOMYCIN SUSPENSION

SOOTHING ACTION . . . Kaolin and pectin coat and soothe the inflamed mucosa, adsorb toxins and help reduce intestinal hypermotility.

BROAD THERAPY . . . The combined antibacterial effectiveness of neomycin and Sulfasuxidine is concentrated in the bowel since the absorption of both agents is negligible.

LOCAL IRRITATION IS REDUCED and control is instituted against spread of infective organisms and loss of body fluid.

PALATABLE creamy pink, fruit-flavored CREMOMYCIN is pleasant tasting, readily accepted by patients of all ages.

*Sulfasuxidine is a trade-mark of Merck & Co., Inc.

MSD **MERCK SHARP & DOHME**
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a new white,

super absorbent

TREATMENT TOWEL

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- Lint free
- Sanitary
- Pure White
- Economical

These treatment towels are not like ordinary towels because they are of three-ply construction and Melamine plastic treated for wet strength. In addition, they are super absorbent, economical, lint free and sanitary. They can be autoclaved and used for sterile drapes. 14x18¼ inches in size . . . pure snowy white and packed 500 to the case.

Write for more information and prices. MM-358a

Physicians & Hospitals Supply Co.

1400 Harmon Place • Minneapolis 3, Minn.

(Continued from Page A-58)

MINNESOTA OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The Minnesota Obstetrical and Gynecological Society will meet on May 3, 1958, in Rochester, Minnesota. Clinical sessions will be held in Mann Hall; surgical clinics, at St. Mary's and Methodist Hospitals.

CONTINUATION COURSES

Medical continuation courses to be presented at the Center for Continuation Study, University of Minnesota are as follows:

March 20-22—Surgery for Surgeons.
March 31-April 2—Gynecology for Specialists.
April 7-9—Radiology for General Physicians.
April 10-12—Arthritis and Physical Medicine for General Physicians.
April 12—Trauma for General Physicians.
April 14-16—Gastroenterology for General Physicians.
May 5-9—Electrocardiography for General Physicians and Specialists.
May 12-16—Proctology for General Physicians.

For further information concerning the above courses, write to the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.

MINNESOTA BLUE CROSS-BLUE SHIELD

(Continued from Page 209)

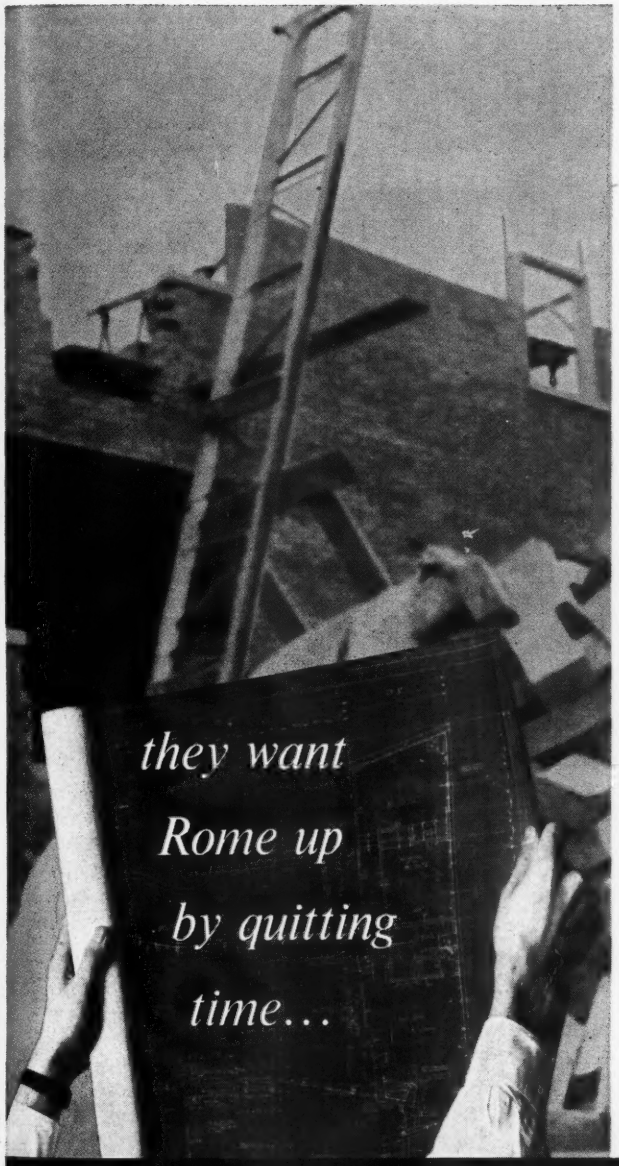
Cross benefits for the treatment of accidental injuries and poisonings.

Conditions relating to pregnancy ranked second in frequency of occurrence among Blue Cross subscribers during the year. Approximately 32,500 patients received Blue Cross benefits totaling over $4,200,000 for confinements and conditions related to pregnancy. During the year, 26,808 Blue Cross babies were born, compared to 24,165 in 1956.

Ranking third in reasons for hospitalization of Blue Cross subscribers, was respiratory illness. As noted, the last quarter upswing in this category resulted in the over-all high incidence rate for total Blue Cross benefits paid to subscribers.

Diseases of the digestive system ranked fourth in the leading reasons for incurred hospital cases during 1957, with approximately 25,000 Blue Cross subscribers being admitted to the hospital. Blue Cross benefits for these cases were higher than in any other category, accounting for approximately $4,800,000 of hospital expense, or 17 per cent of total Blue Cross hospital expense incurred during the year.

Blue Cross membership continued to grow during 1957. As of December 31, 1957, there was a total of 431,337 Blue Cross contracts in effect, representing 1,137,902 participant subscribers. This was a three per cent gain over 1956.



To cut daytime lethargy

(and keep rauwolfia potency)

in treatment of hypertension:

Mounting clinical evidence confirms the view that HARMONYL produces much less lethargy while reducing blood pressure effectively. In the most recent study[1], HARMONYL was evaluated in comparison with reserpine and other rauwolfia alkaloids. HARMONYL *was the only alkaloid which produced a hypotensive response closely matching that of reserpine, coupled with a greatly reduced rate of lethargy.* Only one HARMONYL patient in 20 showed lethargy, while an average of 11 out of 20 showed lethargy with reserpine, and 10 out of 20 with the alseroxylon fraction. Abbott

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for your hypertensives who must stay on the job

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while the drug works effectively . . . so does the patient

1. Comparative Effects of Various Rauwolfia Alkaloids in Hypertension: *Diseases of the Chest*, in press.

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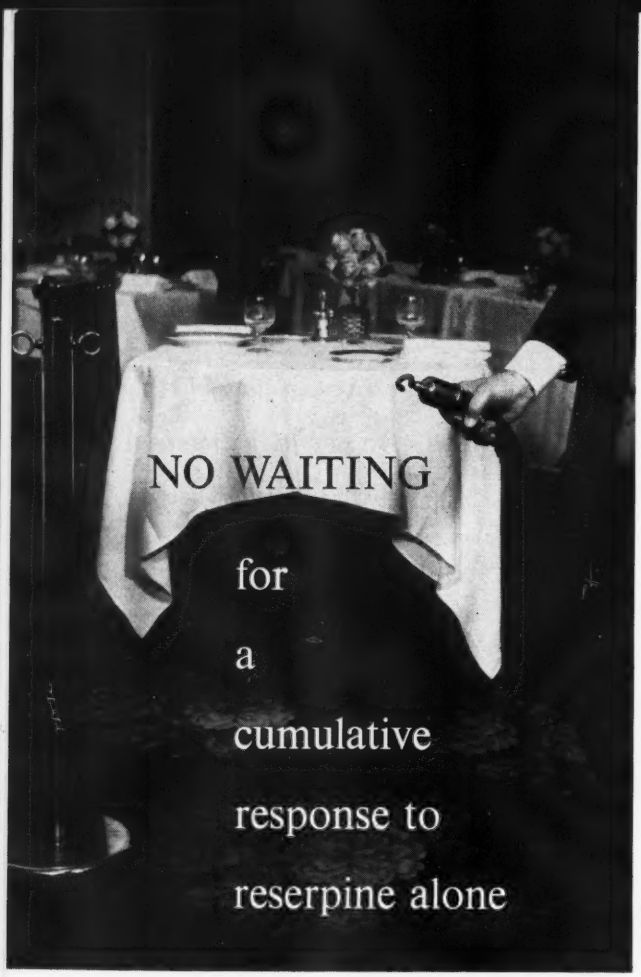


in anxiety and hypertension

NEW *fast-acting*

filmtab®

Harmonyl-N*

(Harmonyl* and Nembutal®)

Calmer days, more restful nights starting *first* day of treatment, through synergistic action of HARMONYL (Deserpidine, Abbott) and NEMBUTAL (Pentobarbital, Abbott). Lower therapeutic doses, lower incidence of side effects. Each HARMONYL-N Filmtab contains 30 mg. NEMBUTAL Calcium and 0.25 mg. HARMONYL. Each HARMONYL-N *Half-Strength* Filmtab combines 15 mg. NEMBUTAL Calcium and 0.1 mg. HARMONYL. Abbott

®Filmtab—Film-sealed tablets, Abbott; pat. applied for

801060 *Trademark

Woman's Auxiliary

WHO NEWS HIGHLIGHTS MID-WINTER BOARD MEETING

The Mid-Winter Board Meeting of the Woman's Auxiliary was held Wednesday, February 5, at the Minnesota Club in St. Paul. Mrs. C. L. Oppegaard presided over the meeting.

The business agenda for the day included a special legislative report by Mrs. L. Raymond Scherer. The possibility of raising dues was also discussed.

Highlight of the meeting was the presentation of a progress report of World Health Organization activities by Dr. Robert N. Barr.

Dr. Barr explained that the tenth anniversary meeting of the World Health Organization will be held in Minneapolis, May 26 to June 14, immediately following the annual auxiliary meeting. The first two days of the observance will be devoted to a tenth anniversary celebration in the Minneapolis Auditorium. An invitation has been extended to President Eisenhower to attend the celebration on May 26.

Dedication of the new Minneapolis Health Center will be held prior to the opening sessions of WHO.

Plenary sessions will begin May 28 and will be held several times each week in the Minneapolis Vocational High School Auditorium. They will break up into individual meetings which will be held at the Leamington and Curtis Hotels in Minneapolis.

Tentative plans include an official reception for WHO delegates at the State Capitol in St. Paul.

Dr. Barr estimated that as many as 22,000 persons representing 88 nations might attend the WHO Assembly, the first ever to be held in the United States.

In addition to the 400 official delegates, there will be the WHO staff from Geneva, representatives of many governmental departments, voluntary health and welfare agencies, and the health workers throughout the nation.

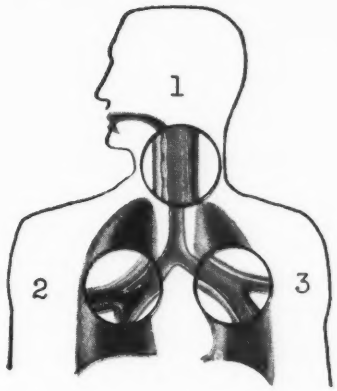
According to Dr. Barr, Minnesota will be the center of world health throughout the assembly. The importance of WHO to peace and stability is recognized by leaders the world over.

Dr. Barr referred to Senators Edward Thye and Hubert Humphrey and to Governor Orville Freeman for their joint untiring efforts to have Minnesota chosen the site of the first United States Assembly of WHO during Minnesota's Centennial Celebration.

The eleventh annual assembly of the World Health Organization in Minneapolis will provide members of the auxiliary an excellent opportunity to actively participate in this observance. Dr. Barr pointed out that plans are to have members of the auxiliary included on the hospitality committees which would be charged with the responsibility of arranging social events in twin city homes for delegates and their wives, during the first weekend of WHO. The following weekend the group will work all day Saturday in order to tour the

(Continued on Page A-64)

breaks up cough*



*Drawing shows how 3-pronged attack of Pyribenzamine Expectorant with Ephedrine breaks up cough by: (1) reducing histamine-induced congestion and irritation throughout the respiratory tract; (2) liquefying thick and tenacious mucus; (3) relaxing bronchioles. Pyribenzamine Expectorant with Codeine and Ephedrine also available (exempt narcotic). Pyribenzamine® citrate (tripelennamine citrate CIBA). **C I B A**

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REDUCE

patient-dosage by

25%

and still get same quality radiographs

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(Continued from Page A-62)

Mayo Clinic on Monday. On the way to Rochester they will visit farms and meet rural Minnesotans. Sightseeing tours of industrial, cultural, medical and educational centers in the twin city area are also planned.

In addition to acting as hostesses for the visitors, the members of the auxiliary were also asked to consider fund-raising methods which would help finance the project.

WOMEN HEMOPHILIC?

For years it was taught that no woman is ever hemophilic, but well-authenticated cases of hemophilia in women are now on record. The disease can appear in a woman when a hemophilic man lives long enough to marry and have children by a woman who is a carrier. Today, a great effort is being made to secure adequate amounts of the antihemophilic globulin which may prevent hemophiliacs from dying of hemorrhages. Such a substance recently has become available.—WALTER C. ALVAREZ, *Modern Medicine*, April 15, 1957.

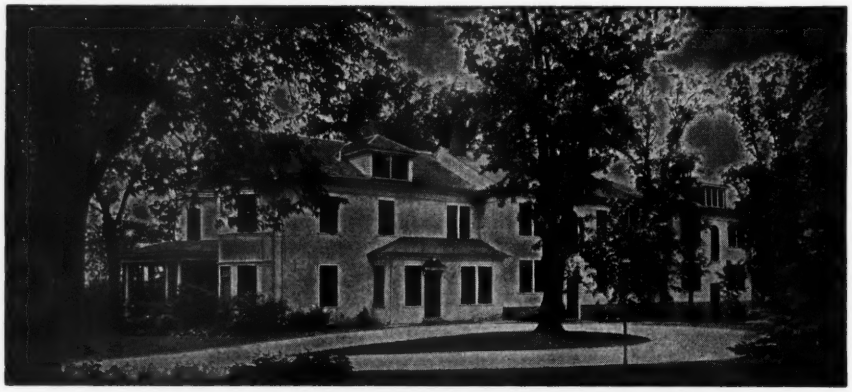
Wilms' tumors comprise 20 per cent of all childhood cancer and 54 per cent appear before the age of three.

* * *

"Pot belly" is a classical sign of Wilms' tumor in children.

* * *

The sooner a patient with Wilms' tumor is diagnosed, the greater the chance for cure.



A MODERN PRIVATE SANITARIUM

for the Diagnosis, Care and Treatment of Nervous and Mental Disorders

MAIN BUILDING—One of 10 Units in "Cottage Plan"

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Located on beautiful Lake St. Croix, 18 miles from the Twin Cities, it has the advantages of both City and Country. Every facility for treatment provided, including recreational activities and occupational-therapy under trained personnel. Close personal supervision given patients, and modern methods of therapy employed. Inspection and cooperation by reputable physicians invited. Rates very reasonable. Illustrated folder on request.

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Superintendent
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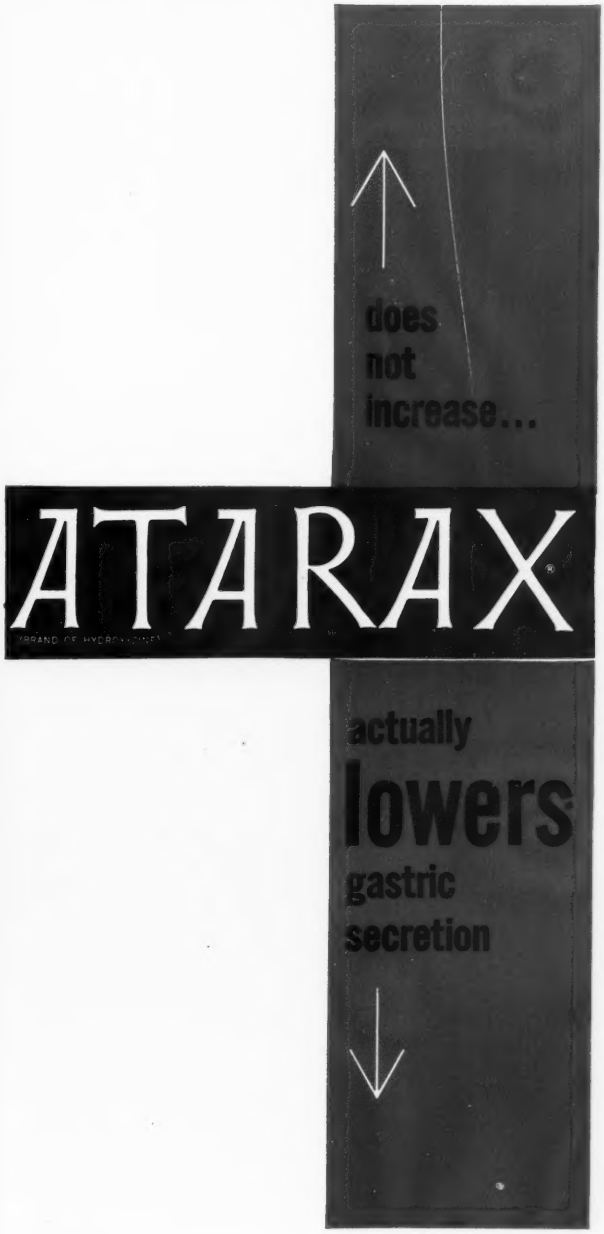
Prescott, Wisconsin
Congress 2-5522

there is one tranquilizer clearly indicated in peptic ulcer...



*Tests in a series of 25 patients show that there is "a definite and distinct lowering [of both volume of secretions and of free hydrochloric acid] in the majority of patients. . . . No patients had shown any increase in gastric secretions following administration of the drug."[1]

Now you have 4 advantages when you calm ulcer patients with ATARAX:

1. ATARAX suppresses gastric secretions; others commonly increase acidity.
2. ATARAX is "the safest of the mild tranquilizers."[2] (No parkinsonian effect or blood dyscrasias ever reported.)
3. It is effective in 9 of every 10 tense and anxious patients.
4. Five dosage forms give you maximum flexibility.

supplied: 10, 25 and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.

references: 1. Strub, I. H.: Personal communication. 2. Ayd, F. J., Jr.: presented at Ohio Assembly of General Practice, 7th Annual Scientific Assembly, Columbus, September 18-19, 1957.

Roerig

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Division, Chas. Pfizer & Co., Inc.

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Secretary

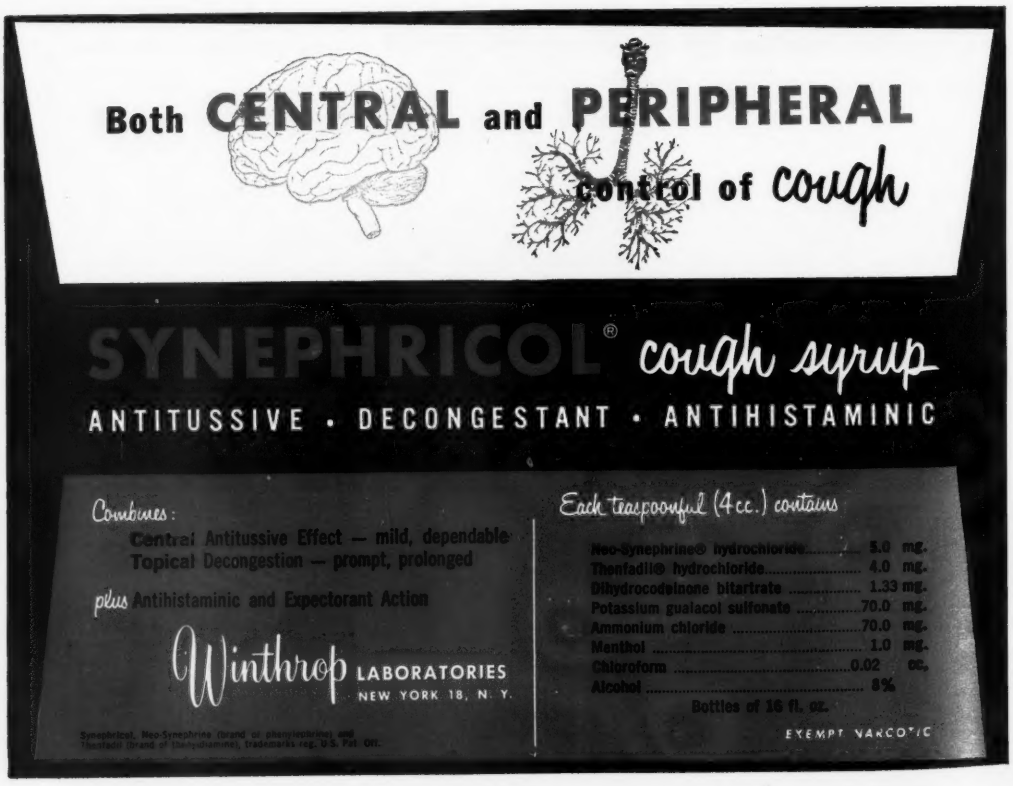
FORMER PHILDELPHIA MAN SENTENCED TO SERVE FIVE-YEAR TERM FOR OBTAINING NARCOTICS BY FRAUD

On January 6, 1958, Simon Manuel Goldberg, thirty-six, 230 Oak Grove Street, Minneapolis, was sentenced by the Hon. Rolf Fosseen, Judge of the District Court of Hennepin County, to serve a term of not to exceed five years in the State Prison at Stillwater for the crime of obtaining narcotic drugs by fraud, deceit, misrepresentation and subterfuge. The defendant, who claimed to have come to Minneapolis recently from Philadelphia, Pa., had obtained eighty-seven tablets of demerol from four Minneapolis physicians by representing that his name was Paul Krueger and that he was suffering from cancer of the stomach and right hip. Goldberg had several scars on his body which he stated were caused by operations for this condition. The defendant had also said that he was a consulting physicist from New York City and that while he was in the Twin Cities in connection with his work he had discovered that he had forgotten to bring with him a sufficient supply of the demerol tablets that his doctor in New York City had been prescribing for him. However, this statement proved to be false.

Two of the Minneapolis physicians who had prescribed demerol for Goldberg became suspicious and notified the authorities after the defendant had left their office but Goldberg was not apprehended until he registered on November 8, 1957, at a Saint Paul hotel, giving his name and address as S. Finley, 240 Central Park South, New York, N. Y. Goldberg was arrested there after he had attempted to obtain narcotic drugs from a Saint Paul physician whom he called to the hotel. Goldberg was then placed in Ancker Hospital, Saint Paul, for observation, and on November 13, 1957, a representative of the Minnesota State Board of Medical Examiners signed a criminal complaint against the defendant which was issued by the Hennepin County Attorney's Office. The defendant waived a preliminary hearing in Minneapolis Municipal Court and then on November 21, 1957, he entered a plea of not guilty before Judge Fosseen in Hennepin County District Court, but on the following day, Goldberg changed his plea to guilty.

The defendant's police record indicates that he first came to the attention of the authorities in July, 1943, when he was held in New York City for a violation of the Selective Service Act. In March, 1949, Goldberg was arrested in Birmingham, Alabama, on a forgery charge and the records show that he was sentenced in Federal Court to serve eighteen months in prison at Tallahassee, Florida. At this time Goldberg was under investigation for impersonating a physicist of the United States Atomic Energy Commission, impersonation of a United States Government employee

(Continued on Page A-68)



MY DAD— HE HURT HIS BACK REAL BAD

"It happened at work while he was putting oil in something"

"He told Mom his shoulder felt like it was on fire"

"He couldn't swing a bat without hurting"

"But Doctor gave him some nice pills--and the pain went away fast"

"Dad said we'd play ball again tomorrow when he comes home"

AND THE PAIN WENT AWAY FAST

FOR PAIN

Percodan®

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC) **TABLETS**

ACTS FASTER...
usually within 5-15 minutes

LASTS LONGER...
usually for 6 hours or more

MORE THOROUGH RELIEF...
permits uninterrupted sleep through the night

RARELY CONSTIPATES...
excellent for chronic or bedridden patients

and now... **NEW**

Percodan®-Demi

VERSATILE

New "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Available through all pharmacies.

Each PERCODAN Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

Literature? Write

Endo®

ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Pat. 2,628,185

(Continued from Page A-66)

with intent to defraud, and falsely obtaining money by impersonating a U. S. Government employee. On January 21, 1950, Goldberg was released on parole from the Federal penitentiary at Lewisburg, Pennsylvania, to which he had been transferred from the prison at Tallahassee, Florida.

In February, 1952, Goldberg was again in the custody of the U. S. Marshall in Washington, D. C., on a check forgery charge and he was sentenced on July 29, 1952, in Federal Court to a prison term of from one to three years. The defendant was sent to the Federal penitentiary at Lewisburg, Pennsylvania, but he was later transferred to the Medical Center for Federal Prisoners at Springfield, Missouri. Subsequently, Goldberg was placed on parole in July, 1953. Goldberg's record reveals that he was again arrested in February, 1955, by the U. S. Marshal in Chicago, Illinois, as a parole violator and returned to the Medical Center for Federal Prisoners from which he was later transferred to the Federal Correctional Institution at Milan, Michigan, where he served the balance of his sentence.

MINNEAPOLIS MAN SENTENCED FOR ILLEGAL SALE OF MEDICINE

On January 3, 1958, Peter J. Toews, seventy-one, 620 South Seventh Street, Minneapolis, was sentenced by the Hon. Victor F. Hanson, Justice of the Peace, in Robbinsdale, Minnesota, for selling a drug and a medicine in a place other than a pharmacy, to a term of thirty days in the workhouse. However, the execution of the sentence was stayed by the Court for a period of one year on condition that the defendant cease the sale of his products. Toews had been charged with the sale of an alleged vitamin food supplement to a Minneapolis woman for the improvement of her general state of health. The defendant admitted that he had sold two ten-ounce bottles of "Green Life" to the woman for the sum of $8.65.

The activities of the defendant were brought to the attention of the Minnesota State Board of Medical Examiners by a doctor of medicine who learned that the defendant was offering to treat a thirty-year-old Minneapolis man who was suffering from multiple sclerosis. When the matter was investigated it was discovered that Toews had assured the patient that one of his products, "Springreen," would be good for the patient's condition. Toews offered to sell a two-months' supply of the product for $58.00, but the patient declined to make the purchase, saying that he would first like to consult with the physician in charge of his case. When further investigation disclosed that Toews had previously made an actual sale of "Green Life" to the woman referred to above, he was charged with an offense in that case.

The defendant admitted in a signed statement that he was engaged in selling two products, "Green Life," which he sold primarily to chiropractors and osteopaths, and "Springreen," which he sold to the general public. Toews stated that both products were very similar and were vitamin food-supplements. Although Toews claimed to be a retired milling company worker, he indicated that he has been engaged in selling various vitamin products since 1951. Toews further stated that his products were purchased from Springreen Products, Inc., 470 Commonwealth Avenue, Boston, Massachusetts.

TAKE A LOOK AT
NEW DIMETANE
THE UNEXCELLED
ANTIHISTAMINE

SAINT PAUL MAN SENTENCED FOR FORGING NARCOTIC PRESCRIPTIONS

On January 16, 1958 Myron A. Seefeldt, forty-six, 1252 Rice Street, Saint Paul was sentenced by the Hon. Arthur A. Stewart, Judge of the District Court of Ramsey County, to a term of not to exceed five years in the State Reformatory for Men at St. Cloud, pursuant to the defendant's plea of guilty on December 11, 1957, to an information charging him with uttering a false and forged prescription calling for 30 cubic centimeters of demerol. However, Judge Stewart then stayed the execution of the sentence and placed Seefeldt on probation for a period of five years and specified that one of the conditions of probation was to be that the defendant shall refrain from the personal use of narcotic drugs unless such drugs should be prescribed for him by a physician.

Seefeldt was arrested on December 3, 1957, in a Saint Paul drug store after he had presented two forged prescriptions for compounding and had received from the pharmacist the parepectolin and a 30 cc. vial of demerol called for by the prescriptions. When the defendant was searched, one hypodermic syringe, two hypodermic needles and a vial containing approximately 12 cc. of demerol were found. A written statement was taken from the defendant after his arrest and he admitted that he had forged the name of a Saint Paul physician, from whom he had stolen some of the prescription blanks, to numerous prescriptions for parepectolin and demerol. According to Seefeldt, he began using narcotic drugs in 1939. When the records of four Saint Paul pharmacies were inspected, it was discovered that the defendant between August 5, 1957, and December 3, 1957, had forged thirteen prescriptions for parepectolin and fifty-five prescriptions for demerol.

On February 19, 1951, Seefeldt was convicted of the crime of grand theft in the Superior Court of Shasta County, California, for which he was sentenced to serve a three year term in San Quentin Prison. He entered the prison on February 22, 1951, was paroled on May 22, 1952, and was declared a parole violator on July 28, 1953. Upon being questioned by Judge Stewart prior to being sentenced, Seefeldt stated that he was presently working as a machinist in Grantsburg, Wisconsin. The Court was informed that the defendant, who had previously submitted to several operations, was suffering from an ailment for which he was under the care of a physician. Judge Stewart stated that in view of the circumstances of this case he had decided to place the defendant on probation.

Sigmoidoscopy is one of the most important parts of the cancer detection examination, and is too often omitted by the general practitioner.

* * *

The place for the examination of persons with symptoms of cancer is the private physician's office rather than a detection center.

* * *

The few cancers found among asymptomatic persons, as well as the high cost of each examination, preclude large-scale financing of cancer detection centers by either governmental or voluntary agencies.

* * *

A well-trained practicing physician can perform in his office all the procedures that are utilized in the cancer detection center provided he has the necessary equipment which he can readily obtain.

Fundamentally most of the cerebellar tumors in childhood are either astrocytomas or medulloblastomas.

Dimetane®
(PARABROMDYLAMINE MALEATE)
TABLETS (4 MG.), ELIXIR (2 MG. PER 5 CC.)
AND EXTENTABS® (12 MG.)
UNEXCELLED
POTENCY, UNSURPASSED THERAPEUTIC
INDEX AND RELATIVE SAFETY. MINIMUM
DROWSINESS AND OTHER SIDE EFFECTS.
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this is Glenhaven

A private, non-sectarian nursing and rehabilitation center, located in Glencoe, Minnesota, 55 miles west of Minneapolis-St. Paul. Glenhaven is planned and equipped to provide complete nursing-home care, including special procedures for persons who require intensive physiotherapy and other rehabilitation treatment.

- *Complete Nursing, Medical, Physiotherapy and Occupational Therapy facilities.*
- *Hospitalization, when necessary, is available at Glencoe Municipal Hospital, directly across the street from Glenhaven.*
- *No limitation on age or sex of residents.*
- *Rates and illustrated brochure available on request.*

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SPACIOUS LANDSCAPED GROUNDS

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Clark W. Truesdale, M. D., Medical Director

General Interest

Lamberton's new resident physician is **Dr. John A. Sturgis.** He will replace **Dr. Morton Roan** who recently retired.

Dr. and Mrs. Roan have taken up temporary residence in Minneapolis where they will remain for several weeks. Although there are no definite plans for the future, the Roans may move to New Mexico where Dr. Roan will continue to practice if his health permits.

* * *

Dr. Hilbert Mark, Minnesota health official, has been named Toledo, Ohio, city health officer.

He has resigned as director of local health administration, the state health department announced.

His successor in the state health department will be **Dr. William C. Harrison,** who has been chief of the section of local health services.

* * *

Dr. Albert J. Schroeder, Minneapolis pediatrician, has been elected chairman of a new medical advisory committee to the Minneapolis public schools health department.

Other committee members, appointed by the Hennepin County Medical Society, are **Drs. Charles Hymes, Harold S. Ulvestad, Frederick G. Rosendahl, Paul W. Linner, William D. Remole, John H. Rosenow** and **James T. Garvey.**

* * *

Dr. Charles Koenigsberger, who has been a physician in Mankato for more than thirty years, was honored by Mankato Clinic doctors and their wives at a party held recently at the Century Club in North Mankato.

* * *

Renville-Redwood Medical Society, at a meeting held recently at Olivia, resolved to resume efforts to get accredited ratings for hospitals at Redwood Falls, Olivia and Sleepy Eye.

The society first voted for the move in May, but plans were deferred here, it was reported, because of labor difficulties. Redwood Falls hospital board in December decided, after a report by **Dr. James B. Flinn,** hospital chief of staff, that accreditation plans not be initiated "at this time."

* * *

Newly elected officers of the Waseca County Medical Society are **Dr. George Olds,** president; **Dr. S. C. G. Oeljen,** vice president; and **Dr. M. C. Florine,** secretary-

(Continued on Page A-73)

when anxiety and tension "erupts" in the G. I. tract...

IN GASTRIC ULCER

PATHIBAMATE*

Meprobamate with PATHILON® Lederle

Combines Meprobamate (*400 mg.*) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of gastric ulcer — without fear of barbiturate loginess, hangover or habituation . . . *with* PATHILON (*25 mg.*) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime. *Supplied:* Bottles of 100, 1,000.

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when you encounter

- respiratory infections
- gastrointestinal infections
- genitourinary infections
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for all tetracycline-amenable infections, prescribe superior

SUMYCIN

Squibb Tetracycline Phosphate Complex

In your patients, **SUMYCIN** *produces:*

1. Superior initial tetracycline blood levels—faster and higher than ever before—assuring fast transport of adequate tetracycline to the site of the infection.

2. High degree of freedom from annoying or therapy-interrupting side effects.

Supply:	*Tetracycline phosphate complex equiv. to tetracycline HCl (mg.)*	*Packaging:*
Sumycin Capsules (per Capsule)	250	Bottles of 16 and 100
Sumycin Suspension (per 5 cc.)	125	2 oz. bottles
Sumycin Pediatric Drops (per cc.—20 drops)	100	10 cc. dropper bottles

SQUIBB

Squibb Quality—the Priceless Ingredient

"SUMYCIN" IS A SQUIBB TRADEMARK

(Continued from Page A-71)

treasurer. The wives of each officer will hold the corresponding position in the association's auxiliary.

* * *

St. Luke's Hospital new chief of staff is **Dr. Joseph F. Bicek.**

Dr. Charles T. Enginton is chief of staff-elect and **Dr. Milton Sorem** is secretary of the medical staff. They were elected at the annual meeting of the hospital's medical staff. Department heads elected for 1958 are: **Dr. James A. Bellomo,** chief of medicine; **Dr. Charles J. Mishek,** chief of general practice; **Dr. Darrell E. Westover,** chief of surgery, and **Dr. Thomas K. Krezowski,** chief of obstetrics-gynecology.

* * *

Minneapolis Swedish Hospital's newly elected Chief of Staff is **Dr. J. Harold Schultz.**

Dr. Wayne C. Rydburg was elected vice president and **Dr. William H. Anderson** was re-elected secretary-treasurer.

* * *

Dr. John Dwyer has been elected chief of staff at Duluth's Miller Memorial Hospital. He succeeds **Dr. Kenneth Teich.**

Other new officers are **Dr. Kenneth Storsteen,** vice chief of staff; **Dr. Harold Walder,** staff secretary. **Dr. Henry Bakkila** and **Dr. Teich,** members of the executive committee. **Dr. Mario M. Fischer,** Duluth and St. Louis county health director, is an ex-officio member of the executive committee.

* * *

"Why the Multiple Health Drives?" was the topic of an address presented by **Dr. John F. Briggs** to the Child Psychology Study circle at its meeting in the Groveland Park School in St. Paul.

* * *

Mayo Clinic doctors have been busy attending national medical and allied field meetings during the past month.

Dr. J. A. Ulrich attended a meeting of the Microbiology Study Section of the National Institutes of Health in New Orleans, January 9-11.

Papers were presented at a meeting of the Neurosurgical Society of America, held at Key Biscayne, Florida, January 15-18, by **Drs. C. B. Holman, C. S. MacCarty** and **Alfred Uihlein. Dr. H. J. Svien** presented a movie which he produced in collaboration with **Dr. Matthew W. Wood. Dr. H. R. Terry** also attended.

Dr. MacCarty's paper was written with **Drs. Milam Leavens, J. G. Love** and **J. W. Kernohan,** and Dr. Uihlein's paper was written with **Drs. H. L. Parker, Alexander Schirger** and **J. W. Kernohan.**

* * *

The Olmsted County Tuberculosis and Health Association became incorporated and adopted by-laws at a meeting of the officers and directors held recently at the Public Health Center.

Under the new incorporation, anyone in the county

when anxiety and tension "erupts" in the G. I. tract...

IN DUODENAL ULCER

PATHIBAMATE*

Meprobamate with PATHILON® Lederle

Combines Meprobamate (*400 mg.*) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of duodenal ulcer — without fear of barbiturate loginess, hangover or habituation . . . *with* PATHILON (*25 mg.*) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime. *Supplied:* Bottles of 100, 1,000.

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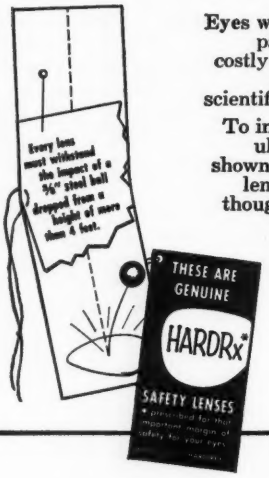
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may apply for membership in the organization and vote at the annual meeting. Heretofore the association has functioned entirely under contract of the State TB Association.

More active interest and participation by residents of the county is desirable, the board stated. The affairs of the county association have gone well, showing a healthy growth of funds available and effective expansion of activities, but more widespread personal interest is sought, however.

The articles provide for rotation of officers and directors and the election of three directors from the county outside of Rochester. Limits were also placed on terms of service.

The previous officers were all re-elected for one-year terms and board of directors was chosen for the 1958-59 year.

Dr. H. Z. Giffin was re-elected president, and other officers renamed are **Dr. C. H. Hodgson**, first vice president; Forest J. Bandel, second vice president; Mrs. E. J. Pomerleau, secretary, and H. E. Tubbs, treasurer. All are of Rochester.

Elected to one-year terms on the board were **Dr. Charles W. Mayo, Dr. John S. Lundy** and Mrs. C. F. Stroebel of Rochester and Mrs. Floyd Stocker of Eyota; two-year terms, Mrs. George B. Logan, **Dr. Viktor O. Wilson** and **Dr. John E. Verby** of Rochester and Mrs. Stanley Hall of Stewartville; three-year terms, **Dr. H. W. Schmidt, Dr. David T. Carr** and **Dr. Alfred G. Karlson** of Rochester and **Dr. A. F. Risser** of Stewartville.

Headquarters for the TB and Health Association will now be at the Public Health Center on Fourth Street S.E. in Rochester.

* * *

Dr. W. A. Fansler of Minneapolis, who is on a world tour, gave a talk Friday, February 21, at the University of Witwaterstrand, Johannesburg, South Africa, on the

topic, "Current Investigations of Polyps of the Rectum and Colon." He presented the same subject on Monday, February 24, at a meeting of the Society of Consultants in Bulawayo, Southern Rhodesia.

Dr. and Mrs. Gordon R. Kamman of St. Paul have recently returned from a six weeks' cruise aboard the S.S. President Wilson. The cruise included stop-overs in China, Japan and Hawaii.

* * *

Drs. R. D. Hanover and **C. B. Will,** International Falls physicians, has moved to quarters in the new building which they constructed at 407 Fourth Street.

The one-story building 37x80 feet, has a decorative brick front set off with large double windows. The structure is built of concrete blocks.

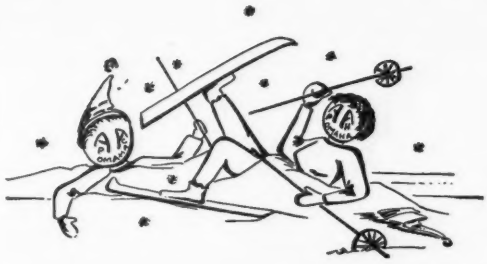
* * *

Dr. Jacob Biedermann, Thief River Falls physician for more than forty years, has discontinued practice due to failing health.

* * *

Dr. John K. Butler, Cloquet, will be installed as chief of medical staff at St. Mary's hospital in Duluth. He succeeds **Dr. D. W. Wheeler,** Duluth.

Dr. Butler, a long-time resident of Duluth, is a graduate of the University of Minnesota medical school and served his internship in St. Mary's Hospital. He has been secretary of the medical staff and was the first member of the staff to serve as chief of the general practice division when it was started in 1953. He is a member of the executive committee of the St. Louis County Medical Society and past president of the Du-



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luth chapter of the American Academy of General Practice. He represents the Minnesota State Medical Association on the World Health Committee of the American Medical Association.

* * *

Dr. Russell T. Brown has purchased the Browerville Clinic from **Dr. A. J. Lenarz.**

* * *

Dr. J. Arnold Bargen, chairman of four sections of medicine in the Mayo Clinic, Rochester, and professor of medicine in the Mayo Foundation, Graduate School, University of Minnesota, is vice chairman of the World Congress of Gastroenterology to be held in Washington, D. C., May 25 to 31, 1958.

* * *

Dr. Bert Eric Schwarz, a fellow in psychiatry of the Mayo Foundation at Rochester from 1951 to 1955, and **Dr. Bartholomew A. Ruggieri,** a fellow in pediatrics at Mayo Foundation from 1952 to 1955, are the authors of a new book for the public entitled "Parent-Child Tensions," published in January, 1958, by the J. B. Lippincott Company of Philadelphia. The book is based on the principles of collaborative psychiatric therapy evolved by Dr. Adelaide M. Johnson, of Rochester, clinical professor of psychiatry in the University of Minnesota. Dr. Schwarz and Dr. Ruggieri are engaged in private practice in Montclair, New Jersey.

* * *

Dr. Harold F. Wahlquist, Minneapolis, was recently named to a new community health board to organize a city-county psychiatric clinic at Minneapolis General Hospital.

* * *

Dr. James Rogers Fox, Minneapolis, was a guest speaker at the meeting of the Zumbrota PTA, early in February. His subject was "Public Health Matters Parents Should Know."

* * *

The following are the officers of the Medical Staff of the St. Cloud Hospital for the year 1958: Dr. L. A. Veranth, Chief of Staff; Dr. C. J. Luckemeyer, Vice President; Dr. R. J. Cesnik, Secretary, and Dr. J. P. O'Keefe, President-Elect.

* * *

Dr. William Sawyer Eisenstadt attended the meeting of the American Academy of Allergy held in Philadelphia, February 1 through 5. During the past year, he served on both the Committee on Aero-Allergens and the Sub-Committee on Weather of the Research Council of the American Academy of Allergy.

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Book Reviews

Books listed here become the property of the Ramsey, Hennepin and St. Louis County Medical Libraries when reviewed. Members, however, are urged to write reviews of any or every recent book which may be of interest to physicians.

COMMON CONTAGIOUS DISEASES. By Philip Moen Stimson, A.B., M.D., Professor of Clinical Pediatrics, Cornell University Medical College, Consulting Pediatrician, New York and Roosevelt Hospitals, Hospital for Special Surgery, et cetera; and Horace Louis Hodes, A.B., M.D., Pediatrician-in-Chief and Director, Department of Pediatrics, Mt. Sinai Hospital, New York; Clinical Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, et cetera. 5th edition. 624 pages. Illus. Price, $8.50. Philadelphia: Lea & Febiger, 1956.

This is the fifth edition of this well-written text or manual first published in 1931. The book has been very thoroughly rewritten for this last edition to bring it up-to-date in every way. It is a very readable and handy text on all aspects of common contagious diseases. The style of the book, a carefully organized table of contents, a cleverly written text, a glossary, index, and even a terminal handy summary chart in the inside of the back cover make it a splendid book for any general practitioner or pediatrician to have in his office. The illustrations and plates are very well reproduced.

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WANTED GENERAL PRACTITIONER—Twin Cities suburban area. New clinic building. Immediate opening. Address E-613, care MINNESOTA MEDICINE.

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References: (1) Greenblatt, R. B., & Clark, S. L.: M. Clin. North America, Philadelphia, W. B. Saunders Company (Mar.) 1957, p. 587. (2) Greenblatt, R. B.: *J. Clin. Endocrinol.* *16*:869, 1956. (3) Hertz, R.; Waite, J. H., & Thomas, L. B.: *Proc. Soc. Exper. Biol. & Med.* *91*:418, 1956.

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